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Adverse Foetal Outcomes in Gestational Diabetes: A Systematic Review and Meta-analysis.

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DECLARATION

I declare that the thesis, *Adverse foetal outcomes in gestational diabetes: a systematic review and meta-analysis* is my work, and has not been submitted for any degree or examination in any other university, and that all the sources used or quoted have been indicated and acknowledged by complete references.

Scholarstica Chinwe Chukwuemeka.

Signature …….....

UWC, Bellville.

October 2020.

ABSTRACT

Gestational diabetes mellitus (GDM) is a condition that affects pregnant women and is one of the most common complications related to pregnancy. According to the World health organisation (WHO), the usual window for diagnosing GDM is between 24 and 28 weeks of gestation and the primary aim of diagnosing gestational diabetes is to identify women and infants at risk of short- or longer-term adverse outcomes. Recent results from the hyperglycaemia and adverse pregnancy outcome (HAPO) study have suggested that even mild levels of hyperglycaemia can have adverse effects on foetal outcomes but there are uncertainties about the prevalence of these outcomes in GDM diagnosed according to the latest WHO 2013 guideline and/or IADPSG 2010 criteria in diverse populations. GDM prevalence has been studied by different researchers, but the prevalence of adverse foetal outcomes in GDM diagnosed based on the latest WHO 2013 guideline and/or IADPSG 2010 criteria have not yet been explored except for the data published by the HAPO study. Due to the lack of sufficient knowledge on foetal outcomes in GDM, this study was conducted to review the evidence on the prevalence of adverse foetal outcomes in GDM diagnosed according to WHO 2013 guideline and/or the IADPSG 2010 criteria.

Different databases including PubMed, Science Direct, Google Scholar and CINAHL as well as bibliographic citations were searched using a well-formulated search strategy to find the relevant observational studies (prospective/retrospective cohort and case-control) using explicit inclusion and exclusion criteria. The following search terms were used, “gestational diabetes”, “pregnancy”, “adverse fetal outcomes” and “adverse foetal outcomes”. The findings of this study were reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and the obtained data analysed using MetaXL ® version 5.3. This review was registered online on PROSPERO, the International prospective register of systematic reviews (registration number: CRD42020155061).

Fifteen studies with 88,831 pregnant women (range: 83-25,543 participants) from 12 countries around the world were identified, with a wide variation in the prevalence of foetal outcomes in GDM using the stipulated criteria. These studies were unevenly distributed geographically as six of them were conducted in Asia, four in Europe, four in North America, one in Australia and none in Africa, Antarctica and South America. A meta-analysis found that the overall prevalence of foetal outcomes ranged from 1% (perinatal mortality) to 11% (large for gestational age). The finding is limited due to the paucity of data on the prevalence of foetal

outcomes in GDM. However, more studies using these criteria in low- and middle- income countries (LMICs) are needed by health care providers, to inform practice and allocate resources for control of GDM and its adverse foetal outcomes in diverse settings and ethnic groups, especially in LMICs.

DEDICATION

I dedicate this work to God Almighty who has made it possible for me to complete this research.

KEYWORDS

Gestational diabetes mellitus

Pregnancy

Prevalence

Adverse Foetal outcomes

Diabetes

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ABBREVIATIONS

ACOG	American Congress of Obstetricians and Gynaecologists
ADA	American Diabetes Association
BMI	Body mass index
BW	Bodyweight
CDA	Canadian Diabetes Association
CINAHL	Cumulative index of nursing and allied health literature
DIPSI	Diabetes in pregnancy study group
FOGSI	Federation of Obstetric and Gynaecological Societies of India
GCK	Glucokinase
GDM	Gestational diabetes mellitus
HAPO	Hyperglycaemia and adverse pregnancy outcome
HbA1C	Glycated haemoglobin test
IADPSG	International Association of Diabetes and Pregnancy Study Group
IDF	International Diabetes Federation
LGA	Large for gestational age
LMICs	Low- and middle- income countries
MODY	Maturity onset diabetes of the young
NDoH	National department of health
NH	Neonatal hypoglycaemia
OGLA	Oral glucose-lowering agents
OGTT	Oral glucose tolerance test
PM	Perinatal mortality
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analysis

PROSPERO	International prospective register of systematic reviews
RDS	Respiratory distress syndrome
SD	Shoulder dystocia
WHO	World Health Organisation

CHAPTER 1

INTRODUCTION

1.1 Background information on Gestational Diabetes Mellitus (GDM)

Diabetes mellitus is a very ancient disease that was first described in 1500 BC by the Egyptian Ebers papyrus. Heinrich Bennewitz in 1824 defined gestational diabetes for the first time in his thesis done in Berlin, Germany (Bennewitz, 1824; Negrato, Mattar and Gomes, 2012). He described a clinical case of a woman with polydipsia and recurrent glycosuria in three successive pregnancies. The woman's urine contained a very substantial amount of saccharine matter (about 60g per 0.20L) during her pregnancies. Then in these successive pregnancies, one of the babies weighed significantly larger than average (almost 5.5kg) (Bennewitz, 1824).

The World Health Organization (WHO) in 1999 defined gestational diabetes mellitus as "carbohydrate intolerance resulting in hyperglycaemia of variable severity with onset or first recognition during pregnancy". From this delineation, the definition of gestational diabetes has been narrowed down by some studies as "glucose intolerance with onset or first recognition during pregnancy," (Metzger *et al.,* 2008). This definition comprises women who had underlying undiagnosed diabetes before pregnancy and those who had normal glucose metabolism before they became pregnant (Kim, 2014). In the interest of moving towards a common standard recommendation for the diagnosis of GDM, the WHO guideline development group decided to accept the general principles behind how the International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria were originated and they decided to adopt these criteria, rather than introduce another set of arbitrary cut-off values. This definition which they adopted only applies to the diagnosis of GDM at any time during pregnancy. The guideline took into consideration the new evidence from the Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) study which involved 25 505 women who underwent an oral glucose tolerance test (OGTT) with blood sampling post 75g oral glucose load (Sacks *et al.,* 2015). Based on this study, the International Association of Diabetes and Pregnancy Study Group (IADPSG) proposed more stringent diagnostic thresholds for GDM (Diabetes care, 2010). It also removed the ambiguity regarding the fasting plasma glucose values in the 1999 WHO guideline (WHO, 2013).

Diabetes in pregnancy is a strong risk factor for future onset of type 2 diabetes (Kim, Newton and Knopp, 2002). It usually occurs in pregnant women whose pancreatic function is inadequate to overcome the insulin resistance resulting from the secretion of diabetogenic hormones by the placenta (Silva *et al.*, 2017). Therefore, GDM has been a controversial clinical problem which can be an indication of relative insulin deficiency and increased insulin resistance. This medical condition has implications for both the baby and the mother (Ali and Dornhorst, 2011), with undesirable outcomes which can affect either the latter or the former.

The prevalence of GDM varies in different populations and is closely related to the prevalence of type 2 diabetes in each population. The prevalence of GDM is also influenced by the definition used and the screening activity for GDM, which makes it difficult to compare prevalence rates between populations (Hunt and Schuller, 2007). In 2015 the International Diabetes Federation (IDF) estimated that there were 415 million (uncertainty interval: 340– 536 million) people aged 20-79years living with diabetes. Out of these, 75% were living in low- and middle-income countries and 5.0million deaths were attributed to this condition. The organization predicted this number to rise to 642 million (uncertainty interval: 521–829 million) people by 2040 (Ogurtsova *et al.*, 2017).

Women with gestational diabetes generally start their treatment with lifestyle modification (diet, exercise and weight management) (Landon *et al*., 2009). This is to say that diet and self-monitoring of blood glucose concentrations are very important factors in the treatment of GDM (Crowther *et al.*, 2005; Langer *et al*., 2005) and can be said to be the first-line treatment for GDM. Pharmacological therapy is introduced only when glycaemic targets are not achieved by lifestyle modification. However, recent studies have shown that other treatment options, such as glucose-lowering agents (metformin, glibenclamide also known as glyburide and insulin), may also play a role in managing the plasma glucose levels of a pregnant woman with GDM (American Diabetes Association, 2004).

1.2 Justification of the study

Despite the increasing impact of GDM, many countries still do not have the epidemiological data which could guide them in responding to the problem Although, recent results from the HAPO study has suggested that even milder levels of hyperglycaemia can result in adverse foetal outcomes (Sacks *et al*., 2015).

There are uncertainties about the prevalence of GDM according to the latest WHO 2013 guideline and/or IADPSG 2010 criteria in a diverse population (Zhu and Zhang, 2016). As a result of this, more studies are required for a comprehensive understanding of the prevalence of foetal outcomes in GDM. This study, therefore, sought to evaluate the prevalence of adverse foetal outcomes in GDM according to the WHO 2013 guideline and/or the IADPSG 2010 criteria.

1.3 Aim of the study

This study aimed to determine the prevalence of adverse foetal outcomes in GDM according to WHO 2013 guideline and/or the IADPSG 2010 criteria using a meta-analysis of existing data. This aim was achieved through the following objectives.

1.4 Objectives

Determine the prevalence of the following adverse foetal outcomes in GDM:

Primary outcomes

- Macrosomia
- Large-for-gestational age (LGA)
- Perinatal mortality

Secondary outcomes

- Shoulder dystocia
- Neonatal hypoglycaemia
- Respiratory distress syndrome (RDS)

1.5 Research Question

This systematic review will answer the following question:

What is the prevalence of adverse foetal outcomes in women diagnosed with GDM using the WHO 2013 guideline and/or the IADPSG 2010 criteria?

1.6 Thesis overview

This first chapter has introduced the topic and presented the background, rationale/objective and research question for this review. It also gave a brief outline of the relevance and perceived justification for conducting this systematic review.

Chapter 2 will extensively discuss what is currently known in the literature regarding GDM. This will be presented in the form of an overview of the literature pertaining to the outlined foetal outcomes of GDM, therapeutic and non-therapeutic treatment, how GDM is diagnosed, the risk factors for GDM as well as the best time of screening for GDM.

Chapter 3 will present the study methodology. This will comprise of the strategy that will be used in the identification of relevant publications, how the selected publications will be managed and assessed for quality and lastly the ethical considerations given for this study.

Chapter 4 will comprise the results of this study. It will outline the findings of the database search and present a report on the study retrieval and screening process, identification of relevant publications and summary of all studies that met the inclusion/exclusion criteria as well as the result of the risks of bias assessment.

Chapter 5 is the concluding chapter of this study. The findings from chapter 4 (the results) will be discussed in light of the objectives of the study. This will be followed by the relevance of these findings to key groups such as the public health sector and lastly the conclusion as well as a summary of the study limitations.

CHAPTER 2

LITERATURE REVIEW

2.1 Gestational diabetes

According to the World Health Organization (WHO) (1999) gestational diabetes mellitus (GDM) refers to "carbohydrate intolerance resulting in hyperglycaemia of variable severity with onset or first recognition during pregnancy". In the year 2013, the WHO categorised hyperglycaemia first detected at any time during pregnancy into the following groups:

- Diabetes mellitus in pregnancy (the diagnosis done here is the same as the diagnostic criteria for diabetes outside of pregnancy).

- Gestational diabetes mellitus (this was categorized as hyperglycaemia lower than the thresholds for diabetes outside of pregnancy, but with a risk of adverse pregnancy outcomes).

With the inclusion of women with known diabetes before pregnancy, the International Diabetes Federation (IDF) used "hyperglycaemia in pregnancy" to describe and classify any glucose intolerance that occurs during pregnancy (Guariguata *et al.,* 2014). GDM is the most common metabolic disorder found in pregnancy (Dornhorst and Frost, 2002; Farrar, 2016) and women with GDM are known to have increased risks of developing type 2 diabetes (Bellamy *et al.,* 2009) with about 35–50% of them developing type 2 diabetes within 10 years after delivery (Tobias, 2018). The recognition, monitoring and appropriate treatment of GDM may help to minimise adverse pregnancy outcomes that may manifest in both mothers and their offspring.

2.1.1 Epidemiology and prevalence of GDM

The prevalence rate of GDM is unknown in many countries and it usually depends on the population studied, individual traits as well as the kind of diagnostic criteria used (Horvath *et al.,* 2010). GDM prevalence is increasing in most countries around the world with the greatest prevalence occurring in women with a family history of the condition, older women, and those with high Body Mass Index (BMI), although this varies among racial or ethnic groups (Ferrara 2007; Jenum *et al.,* 2012). Previous studies from developing countries such as Ethiopia,

Pakistan, Sri Lanka, South Africa, India, Iran, Nigeria and Thailand have found prevalence rates between 0.6% and 18.9% (Ranchod *et al.*, 1991; Hailu and Kebede, 1994; Samad *et al.*, 1996; Siribaddana *et al.*, 1998; Seyoum *et al.*, 1999; Chanpraph and Sutjarit, 2004; Olarinonye, Ohwovoriole and Ajayi, 2004; Keshavarz *et al.*, 2005; Sumeksri, Wongyai and Aimpun 2006; Hossein-Nezhad *et al.*, 2007; Mamabolo *et al.*, 2007). A significant increase in the prevalence of GDM was noted in Australia and the United States, where a higher relative increase was observed in young women**.** A high prevalence was detected amongst Indian-born women (15%) in Melbourne Australia, Zuni Indian women (14.3%), Chinese women (13.9%) and Asian women in Illawarra, Australia (11.9%) (Beischer *et al.*, 1991).

The global prevalence of GDM varies widely, from 1% to 28%, depending on the underlying population characteristics (e.g., maternal age, race/ethnicity, socioeconomic status, or body composition), screening methods, and diagnostic criteria (Jiwani *et al*., 2012). Nonetheless, with rapid urbanisation, decreasing physical activity, changing diets, older maternal age and the trend towards delayed marriage as well as the growing epidemics of obesity and type 2 diabetes, the prevalence of GDM may very well be on the rise.

In 2013, the global prevalence of GDM was estimated to be 16.9%, with low- and middle-income countries contributing about 90% of the cases (Linnenkamp *et al*., 2014). Data from high-income countries showed that the prevalence of GDM ranges from approximately 0.6% to 27.5% (Chiefari *et al*., 2017), while those in low- and middle-income countries were found in the range of 0.4 to 24.3% (Kanguru *et al*., 2014). Recently, a high prevalence of 25.8% was reported among black women from Johannesburg using the IADPSG criteria (Adams and Rheeder., 2017). Another study found a prevalence of 9.1% among black women from Johannesburg (Macaulay *et al*., 2018). Dias and his co-researchers have also shown an increased prevalence of GDM in South Africa using the IADPSG criteria or the WHO 2013 guideline compared with older criteria, which used higher glucose thresholds (Dias *et al*, 2019).

2.1.2 Pathophysiology and pathogenesis of GDM

Glucose requirements increase throughout pregnancy as a result of growing foetal and maternal demands (Angueira *et al.,* 2015). Maternal carbohydrate, protein and fat metabolism changes to ensure that foetal growth and development are well in addition to the material well-being. For this reason, pregnancy induces progressive changes in maternal metabolism with insulin playing a vital role as an important regulator to this (Lowe and Karban, 2014). The hormone insulin helps to control the amount of glucose found in the blood. Depending on individuals, insulin sensitivity may vary, and maternal insulin sensitivity decreases by 50–60% as gestation advances. Insulin resistance seems to be the main factor that leads to GDM. In the second and third trimesters, the levels of hormones such as progesterone placentally derived human growth hormone, cortisol, human placental lactogen, prolactin and other hormones increases (Lain & Catalano, 2007; Salzer, Tenenbaum-Gavish and Hod, 2015). In addition to the hormonal changes, the placenta secretes adipokines such as tumour necrosis factor-alpha and leptin which contributes to postprandial insulin resistance, especially in the peripheral tissues (adipose tissue and skeletal muscle) (McIntyre *et al.,* 2010; Catalano, 2014; Angueira *et al.*, 2015).

In a normal pregnancy, reduction in insulin sensitivity is compensated by adequately increased insulin secretion supposedly from an increased number of pancreatic β-cells from human placental lactogen and prolactin as well as other circulating factors such as the hepatic growth factor (Van Assche, Aerts, and Prins, 1978; Kuhl, 1998; Alvarez-Perez *et al.,* 2014). Maternal fasting glucose levels decrease in the early stage of pregnancy and usually stabilise or begin to rise after 28 weeks of gestation. As the pregnancy develops, insulin resistance and diabetogenic stress resulting from placental hormones result in a compensatory increase in insulin secretion. To maintain glucose homeostasis, concomitant compensation in insulin production is required by the β-cells. During the third trimester, hepatic insulin resistance (resulting in gluconeogenesis) adds further demands on β-cells. To this effect, there is usually a rapid decrease in insulin resistance after delivery, elucidating the role of the placental factors. In situations where this compensation is insufficient, GDM develops (Angueira *et al*., 2015). Most cases of GDM arise from a dysfunction in the beta-cell. This comes as a result of secretions that occur in women with chronic insulin resistance and this condition seems to be related to type 2 diabetes (Buchanan *et al.*, 2007; Lain and Catalano, 2007). β-cell defect is highly hereditary and one of the primary characteristics of GDM (Watanabe *et al*., 2007). Maternal hyperlipidaemia before pregnancy is a contributor to enhancing cytokine expression

and this results in insulin resistance (Catalano, 2014). Hypothetically, women at risk of GDM as a result of metabolic dysfunction that already existed before pregnancy usually have underlying β-cell dysfunction or insulin resistance that surface during pregnancy (Buchanan and Xiang, 2005; Kuhl, 1998). This has led many authors to relate the cause of GDM to insulin deficiency.

From a pathophysiological point of view, gestational diabetes simply implies "reduced maternal insulin sensitivity or increased insulin resistance which appears as a result of a combination of increased maternal adiposity and the insulin-desensitizing". According to Lindsay (2009), the strong family association between type 2 diabetes mellitus and GDM supports the notion that GDM is an inherent abnormality of the β-cell uncovered by the insulin-resistant state of pregnancy.

2.1.3 Signs, symptoms and metabolic changes associated with GDM

According to the NDoH (2018), the classic symptoms of GDM are polyuria (excess and frequent urination), polydipsia (excessive thirst) and polyphagia (excessive hunger). Gestational diabetes symptoms can also be subtle and sometimes difficult to differentiate from some typical pregnancy symptoms found in pregnant women; for instance, it is not unusual for pregnant women to urinate more than usual during pregnancy due to the pressure the foetus places on the bladder. Other possible signs of gestational diabetes include occasional blurred vision due to fluctuations in blood glucose concentration, sores that heal slowly, tingling or numbness in the hands and/or feet, excessive fatigue, weight loss despite increased appetite, frequent infections including those of the bladder, vagina and skin, and dry skin (NDoH, 2018). These symptoms are usually mild and not life-threatening to pregnant women.

2.1.4 Risk factors for GDM

Risk factors for GDM must either relate to impaired insulin secretion and/or contribute directly to the insulin-resistant state. According to Mokdad *et al.* (2003), these risk factors can be classified into 3 main categories based on their clinical characteristics.

High risk

Any of the clinical characteristics mentioned in this category if present in a pregnant woman, exposes them to high risk of developing GDM.

- Marked obesity
- Diabetes in first-degree relative(s) for example parents
- Personal history of glucose intolerance
- Current glycosuria
- Prior delivery of a macrosomic infant

Average risk

Women in this category fit neither in low nor the high-risk profile

Low risk

- Age <25
- No diabetes in first-degree relatives
- Low-risk ethnicity screening not
- No personal history of abnormal glucose levels
- Normal pre-pregnancy weight and pregnancy weight gain
- No prior poor obstetrical outcomes

In addition to the above categories, GDM can occur from interactions between genetic and environmental risk factors (Schneiderman 2010) such as mutations in maturity-onset diabetes of the young (MODY) genes (Eriksson 2007), mutations in glucokinase (GCK) gene and/or dysfunction in the glucokinase gene (Ingelsson *et al.*, 2010).

In a cross-sectional study done with 14,613 women, 722 developed GDM. The population involved women that were without previous GDM and women known to be with diabetes who only reported singleton pregnancy (excluding any pregnancy with twins) for a period of 4 years starting from 1990 to 1994. These were used to measure risk factors for GDM. From the review, it was observed that for maternal age greater than 40 years, a 2 times increased risk of GDM exists compared to women between the ages of 25 and 29 years (Guh *et al.,* 2009)

2.1.5 Diagnosis of GDM

GDM is acknowledged as a burden in most parts of the world and up to date, there are no universally established criteria for GDM screening and diagnosis. There are variations in the diagnostic criteria and screening methods used for GDM all over the world. Some researchers recommend that screening for this disease should start as early as 16 weeks of pregnancy but the majority, practice and recommend screening at 24 to 28 weeks (Seshiah *et al.,* 2008). Generally, early diagnosis of GDM in pregnancy may reveal patients with severe GDM or those with unknown pre-gestational diabetes (Baz, Riveline, and Gautier 2016). It may also permit prompt intervention with prospects for improved perinatal outcomes.

2.1.5.1 Diagnostic criteria for GDM

The recommendations for the screening and diagnosis of GDM vary between medical organisations and health facilities even within the same country (Cutchie, Cheung, and Simmons 2006; Benhalima *et al.,* 2013). The first glucose values used to detect GDM were determined by O'Sullivan *et al*., in 1964 using a 3 hour 100 g Oral Glucose Tolerance Test (OGTT). After investigating the distribution of plasma glucose in pregnant women, these authors suggested the diagnostic criteria that are used for the diagnosis of GDM. The diagnostic criteria were designed to detect pregnant women that are at increased risk of subsequently developing type 2 diabetes after delivery (O'Sullivan and Mahan 1964; Metzger and Coustan, 1998). The diagnosis of GDM depends basically on abnormal OGTT results in pregnancy. The test is usually done after an overnight fast (about 8-14 hours) and then the first blood sample is taken before the patient drinks a sugary drink containing about 75g (or 100 g) anhydrous

glucose mixed with about 250 ml - 300 ml of water. After the glucose load, a 1-hour, 2-hour and sometimes 3-hour venous blood sample is taken (Metzger and Coustan, 1998).

In the interest of developing a universal standard recommendation for GDM diagnosis, the WHO guideline development group decided to agree with the general principles behind how the IADPSG criteria were derived and implement these criteria, rather than introducing another set of the arbitrary cut- off value. This new guideline considers new evidence from the HAPO study, it proposes a new classification for hyperglycaemia first detected in pregnancy (Agarwal, Dhatt and Othman 2015). It also eliminates the ambiguity regarding the fasting plasma glucose values in the 1999 WHO guideline and simplifies certain ambiguities in the IADPSG criteria associated with the ranges of plasma glucose values for distinguishing diabetes in pregnancy and GDM (Diabetes care 2010). Presently, there is no universal agreement over the most appropriate diagnostic criteria for GDM and this variation in the diagnostic criteria has complicated the approach to GDM for many healthcare settings (Agarwal, Dhatt and Othman 2015).

Different diagnostic criteria used in GDM are shown in Table 2.1. The oral glucose tolerance test values are explained in the mmol/L units and each value is measured in whole blood.

Table 2. 1 Different diagnostic criteria used in GDM

Organisation Name	Fasting Plasma Glucose	Glucose Challenge	1-h plasma glucose	2-h plasma glucose	3-h plasma glucose	Number of abnormal values
American Congress of Obstetricians and Gynaecologists (ACOG 2011)	≥5.3	100g OGTT	≥10.0	≥8.6	≥7.8	Two or more values required for diagnosis
World Health Organization (WHO 2013)	≥5.1	75g OGTT	≥10.0	≥8.5	Not required	one value required for diagnosis
International Association of Diabetes and Pregnancy Study Groups (IADPSG 2010)	≥5.1	75g OGTT	≥10.0	≥8.5	Not required	one value required for diagnosis
Canadian Diabetes Association (CDA 2013)	≥5.3	75g OGTT	≥10.6	≥9.0	Not required	Two or more values required for diagnosis
The American Diabetes Association (ADA 2015)	≥5.1	75g OGTT	≥10.0	≥8.5	Not required	Two or more values required for diagnosis

2.1.5.2 Screening for GDM

The ADA, WHO and the ACOG suggest that screening of pregnant women for GDM should be done between the 24th and 28th weeks of gestation especially with pregnant women at high risk of GDM (Agarwal 2015). Early screening (12-16 weeks) is required if any of the high-risk factors are indicated in the women (Kaaja *et al.,* 2013). Late screening identifies more people that have GDM, but it shows fewer people with maternal-foetal risks. Various screening criteria have different explanations for the risk factors, as such a patient may be diagnosed as diabetic based on one set of criteria and non-diabetic based on another set of criteria. Therefore, it can be said that there is no universal/general agreement on the diagnosis of GDM(Agarwal, Dhatt and Othman 2015). The most popular criteria used for diagnosis are the WHO and ADA criteria and these two criteria have undergone numerous revisions over the years. For instance, the WHO criteria which first came into being in 1979 has undergone 4 revisions in the years 1980, 1985, 1999 and 2013.

Criteria limitations: The WHO criteria as well as ADA and ACOG have some limitations which have contributed to the reason why no criterion is widely used. For the WHO criteria, gestational diabetes mellitus is diagnosed only when the criteria for diabetes or impaired glucose tolerance are met. It also uses the same interpretive criteria used for non-pregnant women in diagnosing pregnant women with GDM. In ADA and ACOG (pre-2011) criteria, their cut-offs identify only those women that are at high risk of diabetes after pregnancy.

2.2 Management of GDM

The main objectives for the management of GDM are to achieve tight glycaemic control, prevent any complications that may arise from GDM such as hypoglycaemic coma, hyperglycaemia, and to improve and maintain quality of life. To reach the treatment goals, the HbA1c is the marker often used to monitor patient glycaemia, and patient education is of vital importance in maintaining an ideal adherence to therapy (NDoH, 2018).

2.2.1 Non-Drug therapy

The modalities available for the treatment of GDM are diet, exercise, oral glucose-lowering agents (OGLAs) and insulin of which diet remains the basis of the treatment and lifestyle modification being the cornerstone (Reece and Homko 1998; Jovanovic, 2004). All patients with GDM must try to maintain ideal weight through proper diet and regular exercise such as brisk walking for 30-minutes every day, to help burn off excessive fat. Cessation of smoking (for patients that are smokers) and moderate or no alcohol intake, elimination of sugars from the diet, adjusting energy intake to achieve a weight loss of about 1kg per month as well as eating 2-3 regular meals with balanced energy (kilojoules) is very beneficial as a non-drug therapy for the management of GDM (NDoH, 2018).

2.2.2 Drug therapy

Treatment of GDM remains divisive mostly due to lack of a uniform standard for defining glucose intolerance during pregnancy (Agarwal *et al*., 2005), although metformin and glyburide (glibenclamide) are the oral glycaemic agents of choice when GDM is not controlled by diet (Reece and Homko, 1998). These oral glycaemic agents are becoming a substitute for insulin as they can be administered easily, are not as expensive as insulin (Balsells *et al*., 2015) and do not induce hypoglycaemia and weight gain like insulin (Amin *et al*., 2015).

Insulin

Insulin remains the standard medical treatment agent used in pregnancy for glycaemic control (Bone, 2015). It is used as a supplement in GDM when oral therapy fails to control blood glucose concentrations. Its administration is usually initiated in low doses and increased at frequent intervals until the target values are met, with the quantity of insulin prescribed based on the body weight of the patient. According to Jovanovic (2004), the average daily insulin requirement in pregnancy are 0.7unit/kg body weight per day in the first trimester, 0.8unit/kg body weight per day in the second trimester and 0.9unit/kg body weight in the third trimester.

Fast-acting insulin before meals is administered to control postprandial hyperglycaemia and bedtime basal insulin to control fasting hyperglycaemia. Morning injection of basal insulin may improve glucose balance in some cases (Cheung, 2009). Studies had shown that rapid-acting

insulin analogues (Insulin Lispro and Insulin Aspart) are safe to be used in pregnancy as they present no evidence of increase adverse pregnancy outcomes (Wyatt *et al*., 2005; Aydin *et al.*, 2008; Hod *et al.*, 2008).

Metformin

Metformin belongs to a class of anti-diabetic drug known as biguanides. According to Farrar *et al* (2017), it is commonly used as a first-line drug in the treatment of GDM. It reduces blood glucose concentrations primarily by inhibiting gluconeogenesis in the liver and by increasing glucose uptake in skeletal muscle and adipocytes (Kirpichnikov, McFarlane and Sowers 2002). Although metformin appears to be a safe alternative to insulin therapy, it crosses the placenta, and the clearance of metformin increases in pregnancy (Hughes *et al*., 2006). This has raised concerns regarding its potential adverse effect on the mother and the unborn child. However, metformin does not cause hypoglycaemia or lead to weight gain (Hawthrone, 2006). It increases insulin sensitivity and blood glucose tolerance which makes it a preferred and accepted option in most women with GDM (Hyer *et al*., 2009). It presents more favourable pregnancy outcomes (plus insulin when required) in terms of the risk profile for macrosomia, LGA, RDS and preterm birth although its rate of glucose control is the lowest (Liang *et al*., 2017). It is important to note that metformin (plus insulin when required) achieves slightly better glycaemic control than insulin alone (Farrar *et al*., 2017).

Glyburide

Glyburide (glibenclamide) increases the insulin output from the pancreatic beta cells. It has a half-life of 7 to 10 hours and is broken down by the liver. This drug has a peak concentration of 2-3hours (Anjalakshi *et al.,* 2007). Glyburide is seen as inferior to both insulin and metformin and according to Liang *et al* (2017), Glyburide is associated with more adverse outcomes such as higher birth weight, macrosomia and neonatal hypoglycaemia and therefore should not be used when insulin and metformin are available. Previous reviews also found glyburide had a higher incidence of macrosomia than metformin (Balsells *et al*., 2015; *Jiang et al*., 2015).

2.3 Adverse pregnancy outcomes in GDM

Complications arising from GDM can range from mild to severe, including death. They can be categorised as maternal, foetal or neonatal complications, which may be short term or long term (Salzer and Yogev, 2014). Epidemiological studies suggest that women who are diagnosed with any form of glucose intolerance at any stage during their pregnancy have an increased risk of developing type 2 diabetes later in life (Buchanan and Xiang, 2005; Bellamy *et al*., 2009; Horvath *et al*., 2010). To this effect, early identification of the diabetic status of women with GDM and appropriate treatment can help improve their prognosis and prevent morbidity and mortality in both the women and their offspring.

2.3.1 Primary foetal outcomes

The classification of the foetal outcomes is based on whether the outcome is a direct or an indirect consequence of GDM. The primary outcomes are outcomes that occur as a direct consequence of GDM and these are macrosomia, LGA and perinatal mortality.

2.3.1.1 Macrosomia

Macrosomia is used to describe a new-born with excessive growth. It is the most common and significant morbidity in GDM and has been proven to be associated with increased risk of birth injuries such as shoulder dystocia as well as asphyxia (Persson and Hanson, 1998). Macrosomia is defined as birth weight greater than 4000 g. Infants born with macrosomia are at an increased risk of developing hypertension, type 2 diabetes, birth trauma and obesity in adulthood (McCance *et al*., 1994; Parsons *et al*., 1999; Wei *et al*., 2003; Tian *et al*., 2006). Research studies from different parts of the world have shown that women with GDM commonly give birth to infants with macrosomia. Such studies include a hospital-based study of 42 infants born by women with GDM in Pakistan, with 40.4% of the new-borns born macrosomic (Hussain *et al*., 2011). Another study among 50 infants born by Sudanese women with GDM showed that 28% of the new-borns were macrosomic (Kheir *et al.*, 2012). Similarly, a cohort study of 3,443 pregnant women with GDM in Bahrain showed that 6.5% of the new-borns were also macrosomic with a birth weight of above 4000g (Al Mahroos *et al*., 2005). Macrosomia results in perinatal morbidity and some of its complications may lead to perinatal mortality.

2.3.1.2 Large-for-gestational age (LGA)

Gestational diabetes is the most common cause of LGA (Kim *et al*., 2014). This is usually a result of changes in glucose metabolism of women with GDM which influence the birth weight of their new-borns. The influence of glycaemic change on LGA has been well established in literature with an increased rate of LGA seen in women with an impaired glucose tolerance test (Lao and Ho, 2000). This indicates that glycaemic control serves as a predictive measure for LGA. However, if impaired glucose control is left untreated, there may be an increase in the risk of LGA as seen in a prospective study from Sweden (Östlund *et al.*, 2003). LGA in this study is defined as newborns whose birth weight is greater than the 90th percentile for appropriate gestational age and sex (Dollberg *et al*., 2005).

2.3.1.3 Perinatal mortality

Perinatal mortality was defined as death around the time of delivery which includes both foetal deaths (of at least 20 weeks of gestation) and early infant or neonatal (up to day 7 after birth) death with the vast majority of foetal deaths occurring early in pregnancy (Ventura *et al.*, 2008). In this regard, different studies have shown different trends in perinatal mortality rate and the majority have tried to explain the association between perinatal mortality and GDM. Huddle (2005) reported perinatal mortality of 4.5% in infants born to diabetic mothers. Another study reported a perinatal mortality rate of 90 per 1 000 deliveries in women with diabetes in pregnancy (John, Alegbeleye and Otoide, 2015). There is a need to look at the trends of perinatal mortality in women with GDM since there is a significant improvement in health care and GDM management in many countries all over the world. In addition to perinatal mortality, other adverse foetal outcomes may occur in women with GDM and these are discussed in the next section.

2.3.2 Secondary foetal outcomes

2.3.2.1 Shoulder dystocia

Shoulder dystocia may be defined as “a prolonged head to body delivery time and/or the

necessitated use of ancillary obstetric manoeuvres" (Spong *et al*., 1995). It is an undesirable consequence of foetal macrosomia and occurs when the shoulder fails to be delivered after the delivery of the foetal head. The risk of shoulder dystocia increases as the birth weight increases. For infants weighing between 4000 to 4250g, the risk of shoulder dystocia is about 12.2%, increasing to 16.7% for 4250 to 4500g infants, 27.3% for 4500 to 4750g infants and 34.8% for infants between 4750 and 5000g (Nesbitt *et al*., 1998).

Shoulder dystocia has negative implications for both mothers and babies, with an increase in morbidity and mortality in the former and latter respectively. Common maternal complications are postpartum haemorrhage and fourth-degree laceration into the rectum or unintentional extension of the episiotomy (Gherman *et al*., 1997). Other complications include cervical tears, vaginal lacerations, bladder atony, and uterine rupture (Gherman, 2002). On the other hand, the most common foetal complication resulting from shoulder dystocia is temporary or prominent brachial plexus injuries (Benjamin, 2005). To alleviate shoulder dystocia complications, certain manoeuvres are used, and these include foetal rotational manoeuvres or posterior arm extraction and suprapubic pressure. However, other techniques can also be implemented although they seem to be more aggressive techniques. These include deliberate clavicular fracture, hysterotomy and symphysiotomy (Gherman *et al.*, 2006; Politi *et al*., 2010).

2.3.2.2 Neonatal hypoglycaemia

Neonatal hypoglycaemia is a metabolic abnormality in the new-born which usually arises from the inability of the body to maintain glucose homeostasis (Sperling and Menon, 2004; De *et al.*, 2011). Defining a specific blood glucose concentration for neonatal hypoglycaemia in infants is still a subject of controversy (Cornblath and Ichord, 2000; Laptook and Jackson, 2006; Faustino, Hirshberg and Bogue 2012; Tin, 2014), however, neonatal hypoglycemia may be defined as a plasma glucose level of <1.65 mmol/l in the first 24h of life (Stomnaroska-Damcevski *et al.*, 2015). In some neonates, hypoglycaemia may be transient and asymptomatic which can lead to coma, neonatal seizures and neurologic injury (Suh, Hamby and Swanson 2007; Cloherty, Eichenwald and Stark 2008; Cunningham, Eyal and Gomella 2009). Approximately, 8-30% of neonates born to mothers with GDM have hypoglycaemia with an estimated incidence rate of 27% in infants born to mothers with GDM whereas there is only about a 3% incidence rate among healthy full-term infants born to non-diabetic mothers (Cordero *et al*., 1998; Rozance and Hay, 2006; Maayan-Metzger *et al*., 2014).

2.3.2.3 Respiratory distress syndrome (RDS)

It is generally recognised that new-borns to mothers with GDM are more at risk of developing neonatal respiratory distress (De Luca *et al*., 2009). RDS is caused by a deficiency in lung surfactants (Pickerd and Kotecha, 2009). Around the 24-25th week of gestation, the type 2 pneumocytes start to produce surfactants and by 36-37th week, adequate amounts are produced to support breathing after birth. If there is a lack of surfactants, the alveolar collapses resulting in poorly compliant lungs in the new-born. Infants born with RDS present with respiratory distress within few minutes or hours after birth, and most of them will require supplementary oxygen for support or mechanical ventilation (Crowther *et al*., 2005; Pickerd and Kotecha, 2009). Women with GDM have higher incidence rates of preterm birth compared to the general population. This means their new-borns are at increased risk of developing surfactant-deficient RDS straight after birth (Goldenberg *et al*., 2008; Nabavizadeh *et al*., 2012).

2.3.2.4 Other adverse Foetal outcomes

Low birth weight, birth injury (clavicle fractures and brachial plexus injuries), congenital malformation (anomalies that develop during intrauterine life which can be identified prenatally, at birth, or sometimes during infancy), hyperbilirubinemia, elevated cord blood C-peptide level, and polycythaemia are some foetal outcomes that can be seen in women with GDM (Ju *et al*., 2008; Negrato *et al*., 2012).

2.4 Chapter summary

This chapter has extensively discussed what is currently known in the literature regarding this topic of interest. It presented an overview of the literature on the outlined foetal outcomes of GDM, therapeutic and non-therapeutic treatment, how GDM is diagnosed, the risk factors of GDM as well as the best time of screening for GDM. In the following chapter, the steps taken to obtain the results of this study are discussed.

CHAPTER 3

METHODOLOGY

3.1 Study design

This systematic review and meta-analysis were carried out according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guideline. This guideline provides step-by-step information on the different phases of a systematic review such as the number of publications identified, included and excluded publications, and the reasons for the exclusion. The review was registered online on PROSPERO (CRD:42020155061), the International prospective register of systematic reviews.

3.2 Search strategy for identification of studies

3.2.1 Data sources

A search of the published literature for studies reporting adverse foetal outcomes in offspring born to mothers diagnosed with GDM was conducted. The process of data extraction is explained in section 3.5 of this methodology.

3.2.2 Electronic searches

Electronic databases including PubMed, Science Direct, Google Scholar and CINAHL were searched for information relevant to the objective of this study. A librarian was consulted during the design of the search strategy and the following search terms were used in various combinations and adapted for each database:

“gestational diabetes” “pregnancy” “adverse fetal outcomes” “adverse foetal outcomes”.

Search strategy

The search terms were refined and used to create the following Boolean strings that assisted in the data retrieval process across the four databases that were searched:

1.) ((adverse fetal outcomes OR pregnancy) AND ("gestational diabetes mellitus")).

2.) "adverse fetal outcomes AND gestational diabetes"

3.) (gestational diabetes) AND fetal outcomes.

4.) ((adverse foetal outcomes OR pregnancy) AND ("gestational diabetes mellitus"))

5.) "adverse foetal outcomes AND gestational diabetes"

6.) (gestational diabetes) AND foetal outcomes.

The reference lists of relevant citations for articles of interest were also scanned for further studies.

3.2.3 Inclusion criteria

Types of studies: The systematic review included observational studies (prospective/retrospective cohort and case-control) published from 2009 to 2019 that assessed the prevalence of adverse foetal outcomes in offspring born to mothers diagnosed with GDM.

Study participants: Studies were included in the review if participants were women whose GDM was diagnosed using the WHO 2013 guideline (WHO, 2013) or the International Association of Diabetes and Pregnancy Study Groups (IADPSG, 2010) criteria:

- fasting plasma glucose ≥5.1 mmol/L (92 mg/dL)
- 1-hour plasma glucose ≥10.0 mmol/L (180 mg/dL) following a 75 g oral glucose load
- 2-hour plasma glucose ≥8.5 mmol/L (153 mg/dL) following a 75 g oral glucose load.

Studies included in this review did not restrict participants to a specific age group, and the articles included were not also restricted by language.

3.2.4 Exclusion criteria

Studies were excluded if:

- They were reviews
- They were duplicate publications. (In this case, the article containing the most information was included in the review).
- The studies assessed women diagnosed with diabetes before pregnancy.
- There was no assessment of an outcome relevant to the research question.
- It was an animal study.
- Conference articles

3.3 Types of outcomes

The classification of the foetal outcomes is based on whether the outcome is a direct or an indirect consequence of GDM. The primary outcomes are outcomes that occur as a direct consequence of GDM and the secondary outcomes discussed in this review are not a direct consequence of GDM rather they are outcomes that can emanate from the primary outcomes; e.g shoulder dystocia is an undesirable consequence of foetal macrosomia (Nesbitt., 1998).

3.3.1 Primary outcomes

1. Macrosomia: (birth weight greater than 4000 g). In cases where the birth weights were reported in other units such as kilograms or pounds, a unit conversion was conducted.
2. LGA: Any birth weight above the 90th percentile for gestational age or more.
3. Perinatal mortality: Any death around the time of delivery [including both foetal deaths (of at least 20 weeks of gestation) and early infant (neonatal)] was considered.

3.3.2 Secondary outcomes

1. Shoulder dystocia
2. Neonatal hypoglycaemia
3. RDS.

3.4 Risk of Bias

The risk of bias for each included study was assessed using the Hoy 2012 tool with ten parameters addressing internal and external validity (Hoy *et al*., 2012). The tool consists of ten parameters which address four areas of bias and an eleventh item which provides the summary of the risk of bias assessment. Each parameter was evaluated as either low, moderate or high risk of bias (Table 3.1). “Unclear” was considered as high risk of bias. Studies were classified as having a low risk of bias when eight or more of the ten questions were answered as ‘‘yes (low risk)’’, a moderate risk of bias when six to seven of the questions were answered as ‘‘yes (low risk)’’ and a high risk of bias when five or fewer questions were answered as ‘‘yes (low risk)’’.

Table 3. 1 Risk of bias assessment tool.

1. Representation Was the study population a close representation of the national population?	• Yes (low risk) • No (high risk) • Unclear
2. Sampling Was the sampling frame a true or close representation of the target population?	• Yes (low risk) • No (high risk) • Unclear
3. Random selection Was some form of random selection used to select the sample OR was a census undertaken?	• Yes (low risk) • No (high risk) • Unclear
4. Non-response bias Was the likelihood of non-response bias minimal?	• Yes (low risk) • No (high risk) • Unclear
5. Data collection Were data collected directly from the subjects?	• Yes (low risk) • No (high risk) • Unclear
6. Case definition Was an acceptable case definition used in the study?	• Yes (low risk) • No (high risk) • Unclear
7. Reliability and validity of study tool Was the study instrument that measured the parameter of interest shown to have reliability and validity?	• Yes (low risk) • No (high risk) • Unclear

8. Data collection Was the same mode of data collection used for all subjects?	• Yes (low risk) • No (high risk) • Unclear
9. Prevalence period Was the length of the prevalence period for the parameter of interest appropriate?	• Yes (low risk) • No (high risk) • Unclear
10.Numerators and denominators Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	• Yes (low risk) • No (high risk) • Unclear

3.5 Data extraction and management

Citations of the search results from the databases and websites using the search terms mentioned above were imported into Mendeley, and duplicates were removed. Articles whose titles and/or abstracts were not related to the study were then excluded, and the remaining eligible articles based on the inclusion criteria were retrieved. Data in the form of authors and year of publication, the country where the study was conducted, the ethnicity of study participants, study design, the total number of participants with GDM according to WHO 2013 guideline and/or IADPSG 2010 criteria, maternal BMI, foetal outcomes, the prevalence of GDM in the population, and the number of participants affected by each outcome was extracted from eligible articles into a data extraction form in Microsoft Office Excel (which was later converted into a word document) and this is shown in Table 4.1. The foetal outcomes were specifically macrosomia, LGA, perinatal mortality, shoulder dystocia, neonatal hypoglycaemia and RDS. The reviewer checked for the completeness as well as the accuracy of extracted data.

3.6 Data synthesis and analysis

The data were analysed using MetaXL ® version 5.3 (Barendregt and Doi, 2016). Random effects models were used to estimate the pooled prevalence for each outcome as we expected a lot of heterogeneity between studies. Forest plots were used to depict the prevalence and 95% confidence interval (95% CI). Heterogeneity was assessed using Cochran's Q statistics and quantified using the I^2 statistic based on the following standard criteria; 0% (no heterogeneity) to 100% (highest heterogeneity). I^2 values greater than 50% was classified as substantial heterogeneity and above 75% indicated high heterogeneity.

3.7. Assessment of publication bias

Doi plots and funnel plots were used to check the existence of any publication bias. The graphical display (Doi plot) and a quantitative measure (LFK index) dictated study asymmetry in this meta-analysis. The closer the value of the LFK index to zero, the more symmetrical the Doi plot would be and zero represents complete symmetry. Values beyond ±1 were deemed consistent with asymmetry. The plot was supplemented with formal statistical testing using the Begg's test (Begg CB and Mazumdar M., 1994) and the Egger test (Egger M and Smith GD., 1997). Publication bias occurs when results of published studies are systematically different from results of unpublished studies and it is one of many possible explanations for an asymmetric funnel plot in meta-analysis.

3.8 Ethics

This study used data from published studies and did not use data from individual participants. No data set was shared or obtained from authors of original publications. Therefore, ethics review and informed consent from participants were not necessary.

3.9 Chapter summary

Each of the sections in this chapter has discussed the methodological process taken in identification relevant publication, how these articles were assessed for quality and included in this review. In the next chapter, the findings of this adopted process will be outlined.

CHAPTER 4

RESULTS

4.1 Description of the literature search

An electronic search of four databases (PubMed, Science Direct, Google Scholar and CINAHL) using the search terms “gestational diabetes”, “pregnancy”, “adverse fetal outcomes” and “adverse foetal outcomes” was conducted, and it resulted in the identification of 4362 publications. Following the removal of duplicate publications (n=420), 3942 publications were retrieved for a preliminary assessment. Preliminary screening of titles and abstracts of the 3942 publications yielded 24 potential publications. Of these 24, three were conference articles and were excluded, while full-text articles of the remaining 21 publications were obtained and evaluated against the study’s inclusion criteria. Eleven publications were found eligible, and an additional four eligible publications identified following the screening of the reference lists of the included publications to yield a total of 15 eligible publications, which were included in the meta-analysis. Figure 4.1 presents a flowchart of the process of identification of eligible publications and table 4.1 presents characteristics of included publications. The list of excluded articles with reasons for exclusion is presented in appendix I.

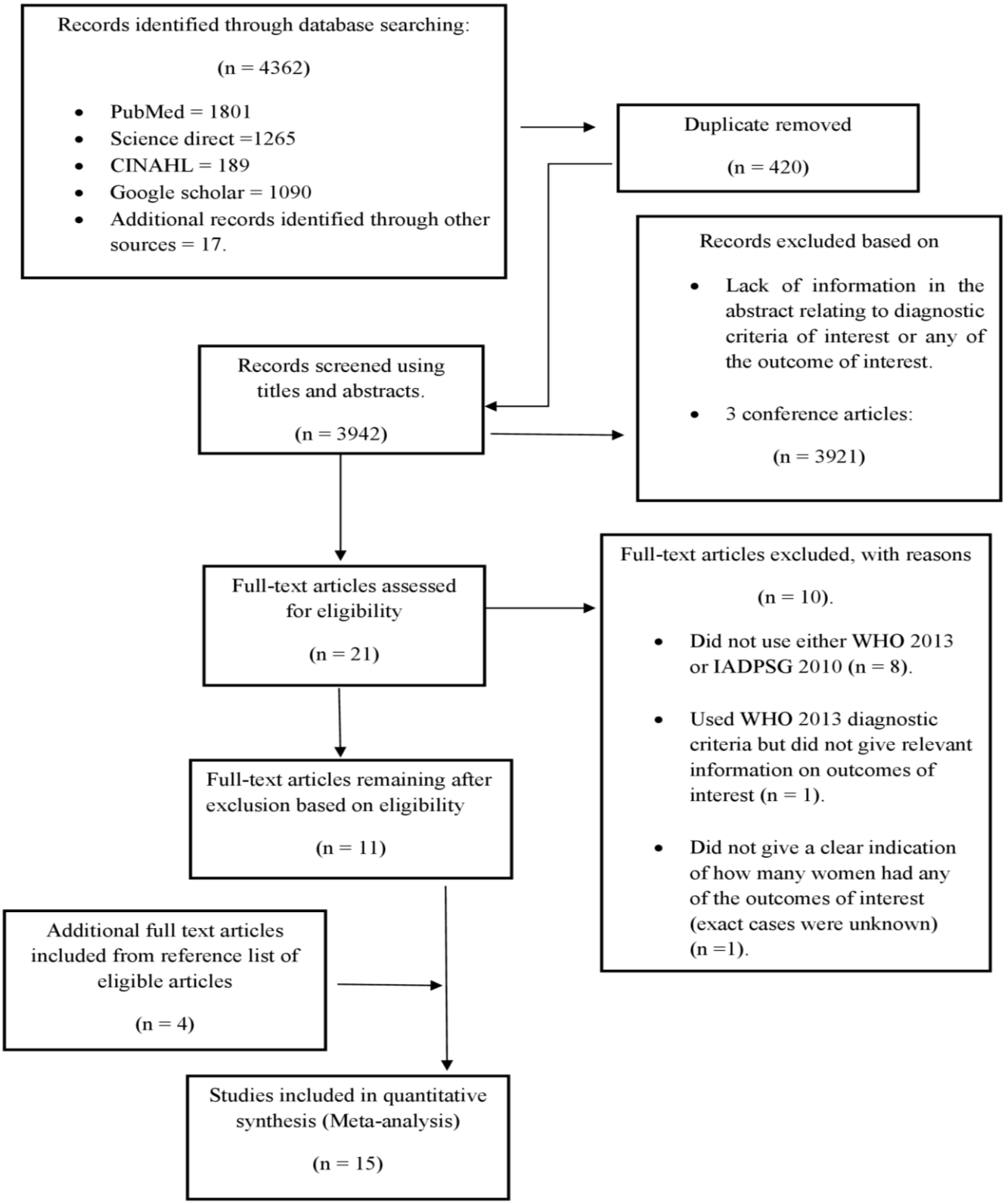

Figure 4. 1 PRISMA flow diagram of selection of publications.

4.2 Characteristics of included studies

Of the 15 included publications, 11 were retrospective cohort studies, 3 were prospective cohort studies and one study was a case report. Two studies each were performed in Canada (Bodmer *et al*., 2012; Kong *et al*., 2015), the United States of America (March *et al*., 2016; Sacks *et al*., 2015), and India (Uma *et al*., 2017; Nayak *et al*., 2013). One study each was performed in the United Kingdom (Meek *et al*., 2015), Japan (Ikenoue *et al*., 2014), Vietnam (Hirst *et al*., 2012), Western Australia (Laarfira *et al*., 2016), Ireland (O'Sullivan *et al*., 2011), Belgium (Oriot *et al*., 2018), Italy (Corrado *et al*., 2016), China (Liao *et al*., 2014) and Taiwan (Wu *et al*., 2016). All fifteen included publications provided information on at least one of the adverse foetal outcomes of interest and the pregnant women were diagnosed with GDM according to the WHO 2013 criteria or the IADPSG 2010 guideline (75g OGTT with fasting glucose ≥ 5.1mmol/l, 1hour ≥10.0mmol/l, ≥ 2hours 8.5mmol/l). The included publications were published between 2009 and 2019 with a total sample of 88,831 pregnant women (with a minimum sample size of 83 and maximum sample size 25,543) in 12 countries. A map displaying the location and the total number of participants from the included studies are presented in Figure 4.2. although, the total number of participants from studies done in Canada (Bodmer *et al*., 2012 and Kong *et al*., 2015) and India (Uma *et al*., 2017 and Nayak *et al*., 2013) were merged and represented as a sum (Canada: 5411+22397= 27808, India: 1124+83= 1207) on the map. However, the total number of participants from the two studies from the USA (Boston: 235 and Southern California: 9835) were placed separately on the map.

Table 4. 1 Characteristic of included studies.

Study citation	Study characteristics				Foetal characteristics					
	Country and study design	Total number of participants*	Ethnicity	Reported GDM Prevalence*	number with macrosomia (macrosomia diagnosis)	number with LGA	number with perinatal mortality	number with neonatal hypoglycaemia	number with RDS	number with shoulder dystocia
Bodmer-Roy *et al.*,2012	Canada (retrospective observational study)	5411(186)	Not reported	27.51	Not reported	17	Not reported	4	Not reported	2
Laarfira *et al.*,2016	Western Australia (retrospective study)	3571(559)	Caucasian, Aboriginal, Asian, Indian, Maori, African	16	60(≥4000g)	Not reported	3	Not reported	Not reported	Not reported
Corrado *et al.*, 2016	Italy (retrospective study)	411(379)	Caucasian	Not reported	33(>4000g)	Not reported	Not reported	8	Not reported	Not reported
Oriot *et al.*, 2018	Belgium (retrospective study)	3754(691)	Belgian	18.4	Not reported	33		Not reported	Not reported	Not reported

Kong *et al.*, 2015	Canada (retrospective study)	22397(2104)	Not reported	9.4	Not reported	254	Not reported	33	Not reported	Not reported
Liao *et al.*, 2014	China (retrospective study)	5360(1314)	Chinese	24.5	22(≥4000g)	64	Not reported	18	52	Not reported
March *et al.*, 2016	USA (retrospective cohort study)	235(104)	Not reported	44.3	12(>4000g)	Not reported	Not reported	3	Not reported	1
Meek *et al.*, 2015	United Kingdom (retrospective study)	25543(1181)	White, Black, Asian, others	4.62	243(>4000g)	310	Not reported	Not reported	Not reported	Not reported
Sacks *et al.*, 2015	Southern California (retrospective cohort study)	9835(771)	Non-Hispanic white, Black, Latina, Asian or pacific islander, other/unknown	9.9	Not reported	120	Not reported	5	14	19
Uma *et al.*, 2017	India (case report/series)	1124(212)	Not reported	Not reported	16(birth weight >90th percentile)	Not reported	1	7	Not reported	Not reported
Wu *et al.*, 2016	Taiwan (retrospective study)	1840(952)	Asian	13.44	Not reported	Not reported	1	5	Not reported	Not reported

O'Sullivan *et al.*, 2011	Ireland (prospective study)	5500(680)	Not reported	Not reported	33(>4000g)	149	Not reported	16	24	8
Hirst *et al.*, 2012	Viet Nam (prospective cohort study)	2772(550)	Vietnamese	Not reported	Not reported	62	3	9	Not reported	Not reported
Nayak *et al.*, 2013	India (prospective cohort study)	83(72)	Not reported	27	Not reported	1	2	Not reported	3	Not Reported
Ikenoue *et al.*, 2014	Japan (retrospective cohort study)	995(141)	Not reported	Not reported	1(>4000g)	10	Not reported	Not reported	Not reported	Not reported

*In the column with the total number of participants, the numbers in bracket represents the number of women diagnosed with GDM using WHO 2013 and IADPSG 2010 criteria.

*The prevalence in the above Table 4.1 were reported from the prevalence given by the different authors of the included publications.

Figure 4. 2 Map displaying the location and the total number of participants from the included publications.

4.3 Risk of bias and quality assessment

The risk of bias for each study was assessed in ten different domains using the Hoy risk of bias tool (Hoy *et al*., 2012) and the results are shown in Table 4.2. All the studies used standardized methods for diagnosing gestational diabetes and due to the initial quality screening, all included studies in the final review were of either moderate or high risk of bias. Of the 15 included studies, the summary assessment was of a moderate risk of bias for 4 studies (26.7%) (Liao *et al*, 2014; Kong *et al*, 2015; Meek *et al*, 2015; Uma *et al*, 2017) and high risk of bias for 11 studies (73.3%) (O'Sullivan *et al.*, 2011; Bodmer-Roy *et al*., 2012; Hirst *et al.*, 2012; Nayak *et al.*, 2013; Ikenoue *et al.*, 2014; Corrado *et al.*, 2016; Laafira *et al.*, 2016; March *et al.*, 2016; Wu *et al*., 2016; Sacks *et al.*, 2015; Oriot *et al.*, 2018). Most of the studies showed a high risk of bias with respect to representativeness.

Table 4. 2 Risk of bias assessment of included studies using the Hoy 2012 tool.

Citation	Represen-tation	Sampling	Random selection	Non-response bias	Data collection	Case definition	Reliability of tool	Method of data collection	Prevalence period	Numerators and denomi-nators	Summary assessment
Bodmer Roy *et al.*,2012.	high	unclear	high	unclear	low	low	Unclear	low	low	unclear	High
Laarfira *et al.*, 2016.	high	low	high	unclear	low	low	Unclear	low	low	unclear	high
Corrado *et al.*, 2016.	high	high	high	unclear	low	low	Low	low	low	unclear	high
Oriot *et al.*, 2018.	high	high	unclear	unclear	low	low	Unclear	low	low	unclear	high
Kong *et al.*, 2015.	high	unclear	low	unclear	low	low	Low	low	low	unclear	moderate
Liao *et al.*, 2014.	high	high	low	unclear	low	low	Low	low	low	unclear	moderate

March *et al*., 2016.	high	unclear	high	unclear	low	low	low	low	low	unclear	high
Meek *et al*., 2015.	high	low	low	unclear	low	low	unclear	low	low	unclear	moderate
Sacks *et al*., 2015.	high	low	high	unclear	low	low	unclear	low	low	unclear	high
Uma *et al*., 2017.	high	unclear	low	unclear	low	low	low	low	low	unclear	moderate
Wu *et al*., 2016	high	high	high	unclear	low	low	unclear	low	low	unclear	high
O'Sullivan *et al*., 2011.	high	unclear	low	unclear	low	low	unclear	low	low	unclear	high
Hirst *et al*., 2012.	high	high	low	unclear	low	low	unclear	low	low	unclear	high
Nayak *et al*., 2013.	high	unclear	low	unclear	low	low	unclear	low	low	unclear	high
Ikenoue *et al*., 2014.	high	unclear	low	unclear	low	low	unclear	low	low	unclear	high

4.4 Prevalence of foetal outcomes

4.4.1 Macrosomia

Of the fifteen included studies, eight studies reported data on macrosomia. Macrosomia prevalence ranged from 1% (95%CI: 0 to 3) in Japan (Ikenoue *et al*., 2014) to 21% (95%CI:18 to 23) in the United Kingdom (Meek *et al*., 2015). Figure 4.3 presents the pooled estimates of prevalence and 95% confidence intervals (CI) after meta-analysis. Random-effects analysis indicated an overall prevalence of 7% (95%CI: 2 to 13) with significant heterogeneity between the studies (I^2 = 98%). A funnel plot including all studies on macrosomia was generated (Figure 4.4) and the Doi plot for publication bias showed no asymmetry (LFK index = -0.51) (Figure 4.5). Therefore, publication bias is unlikely.

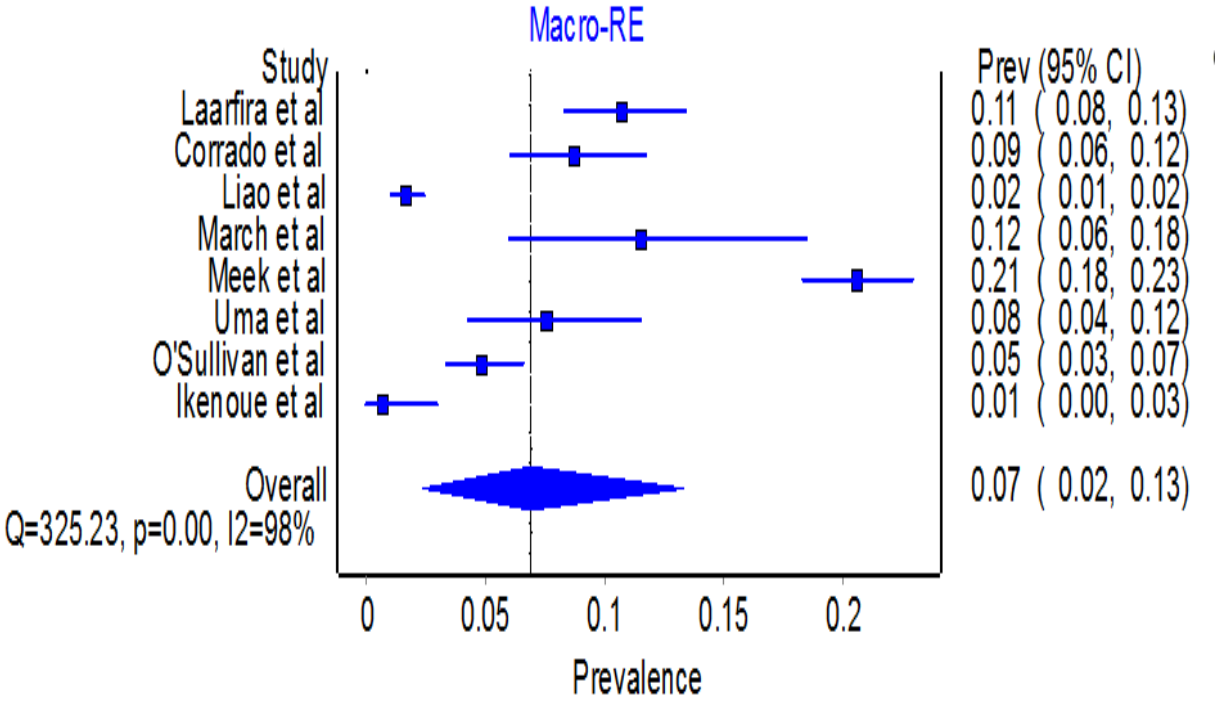

Figure 4. 3 Forest plot showing the meta-analysis for the prevalence of macrosomia.

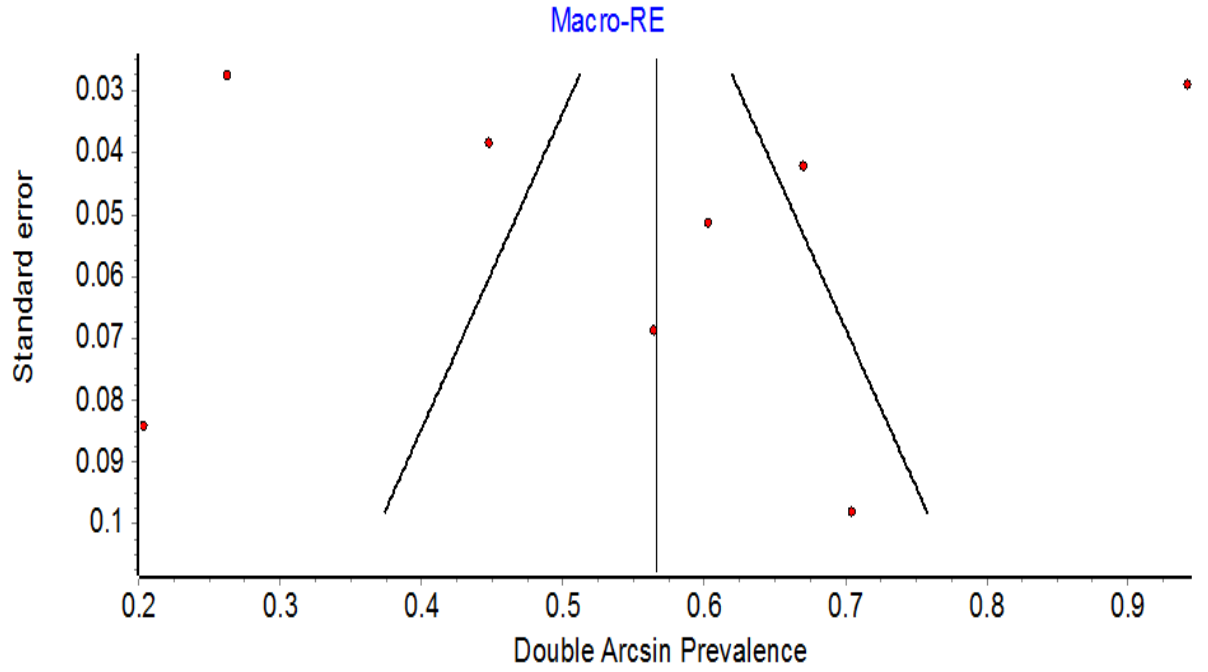

Figure 4. 4 Funnel plot for macrosomia

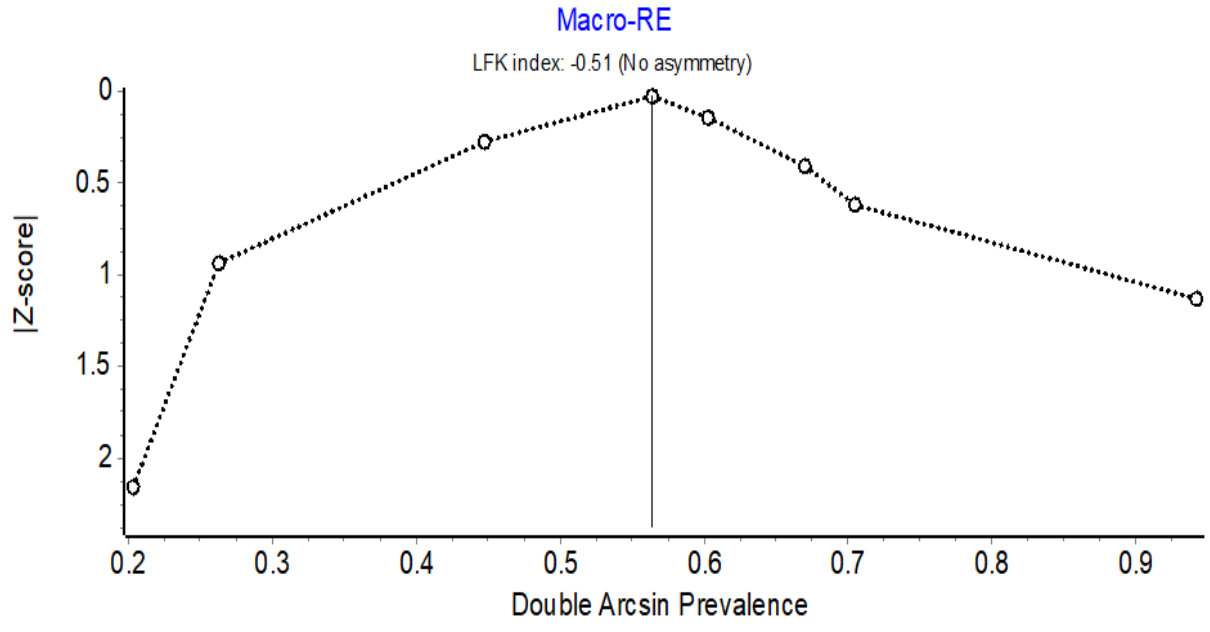

Figure 4. 5 Doi plot and LFK index of publication bias for macrosomia.

4.4.2 Large-for-gestational age (LGA)

Ten studies reported on the prevalence of LGA ranging from a minimum of 1% (95%CI: 0 to 6) in India (Nayak *et al.*, 2013) to a maximum of 26% (95%CI: 24 to 29) in the United Kingdom (Meek *et al.*, 2015). A random-effects meta-analysis yielded an overall prevalence of 11% (95%CI: 6 to 16) with substantial heterogeneity between the studies (I^2 = 98%) (figure 4.6).

A funnel plot including all studies on LGA was generated (Figure 4.7) and the Doi plot for publication bias showed minor asymmetry (LFK index = -1.56) (Figure 4.8) which could be an indication of possible publication bias.

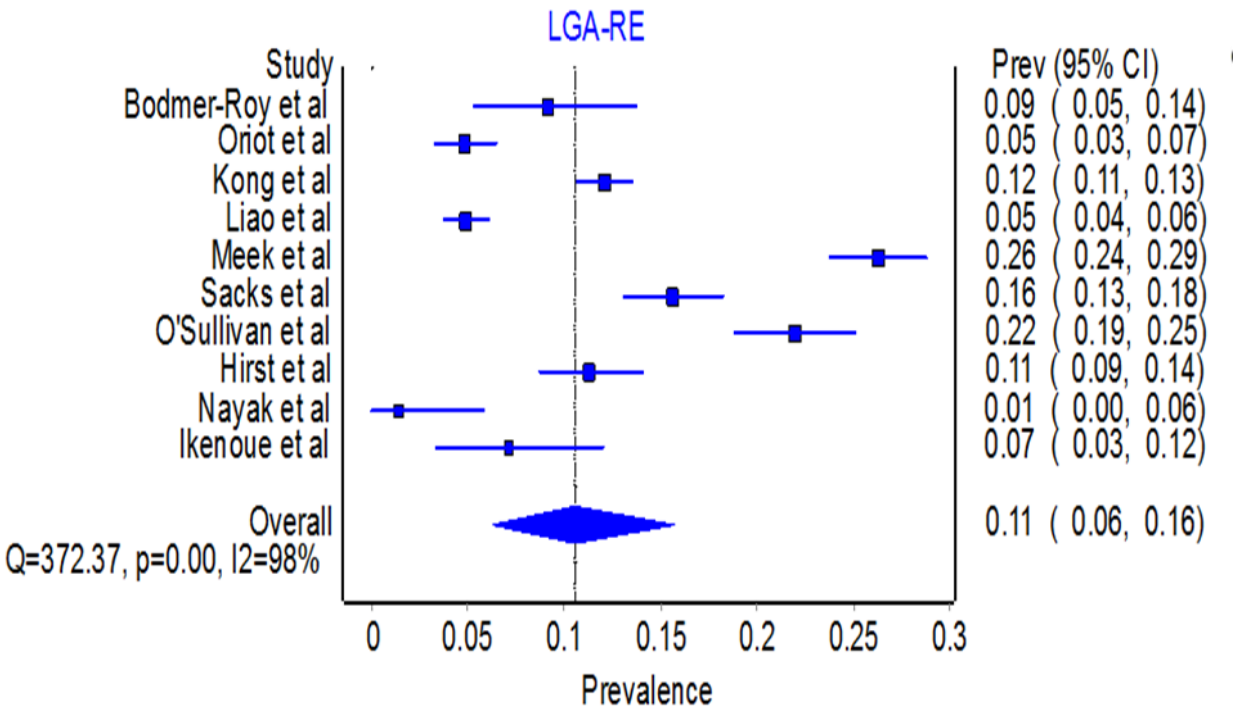

Figure 4. 6 Forest plot showing the meta-analysis for the prevalence of LGA.

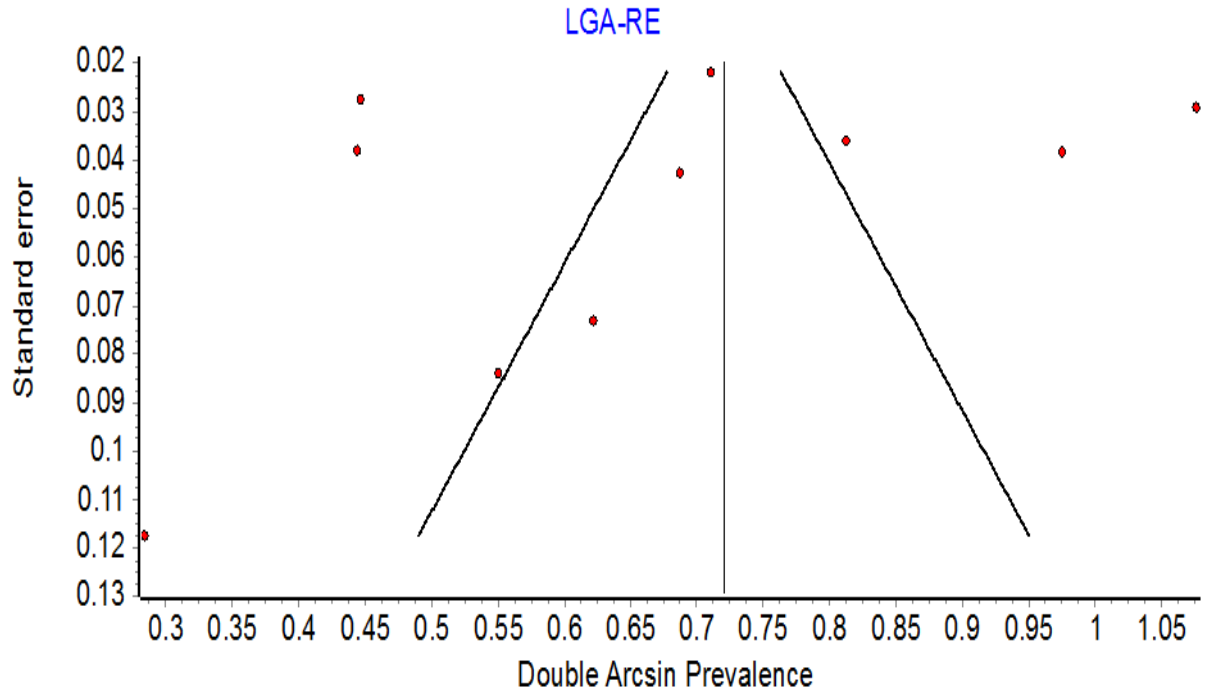

Figure 4. 7 Funnel plot for LGA.

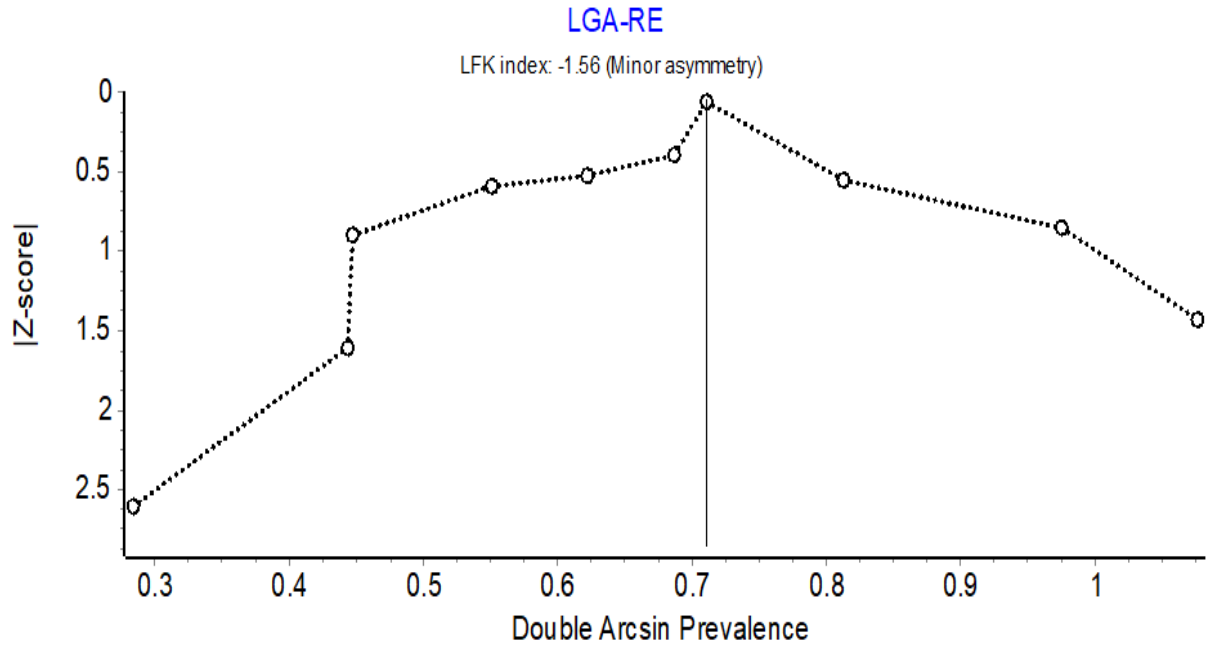

Figure 4. 8 Doi plot and LFK index of publication bias for LGA.

4.4.3 Shoulder dystocia

Three studies reported on the prevalence of shoulder dystocia. Two of these studies found a minimum prevalence of 1% in the United States of America (95%CI: 0 to 4) (March *et al*., 2016) and Ireland (95%CI: 0 to 2) (O'Sullivan *et al.,* 2011). The maximum prevalence of shoulder dystocia of 2% (95%CI: 1 to 4) was reported in the United States (Sacks *et al*., 2015) (figure 4.9). A random-effects meta-analysis yielded an overall shoulder dystocia prevalence of 2% (95%CI: 1 to 3) with little heterogeneity (I^2 = 42%). A funnel plot including all studies on shoulder dystocia was generated (Figure 4.10) and the Doi plot for publication bias showed no asymmetry (LFK index = 0.76) (Figure 4.11). Therefore, publication bias is unlikely.

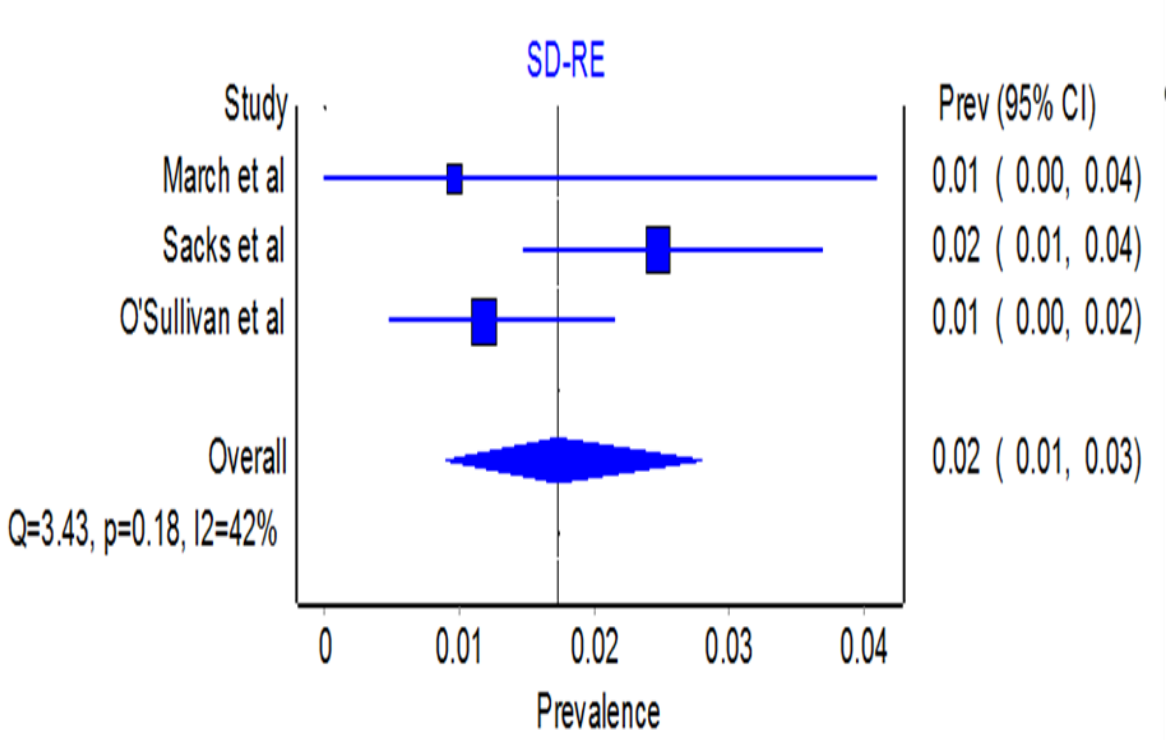

Figure 4. 9 Forest plot showing the meta-analysis for the prevalence of shoulder dystocia.

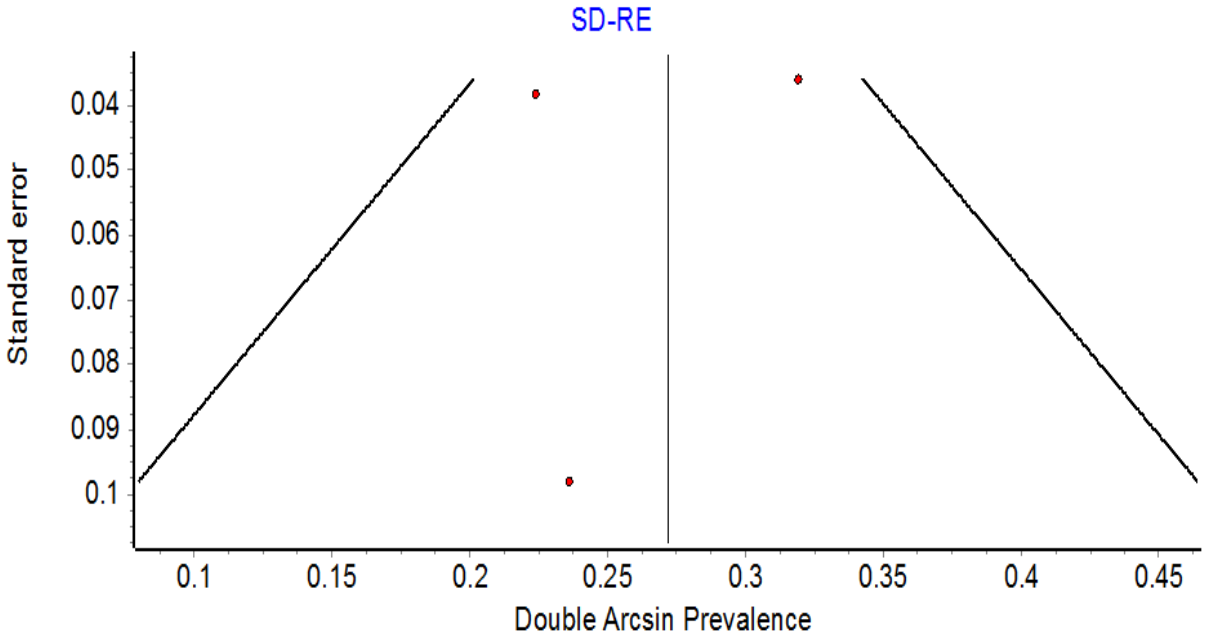

Figure 4. 10 Funnel plot for shoulder dystocia.

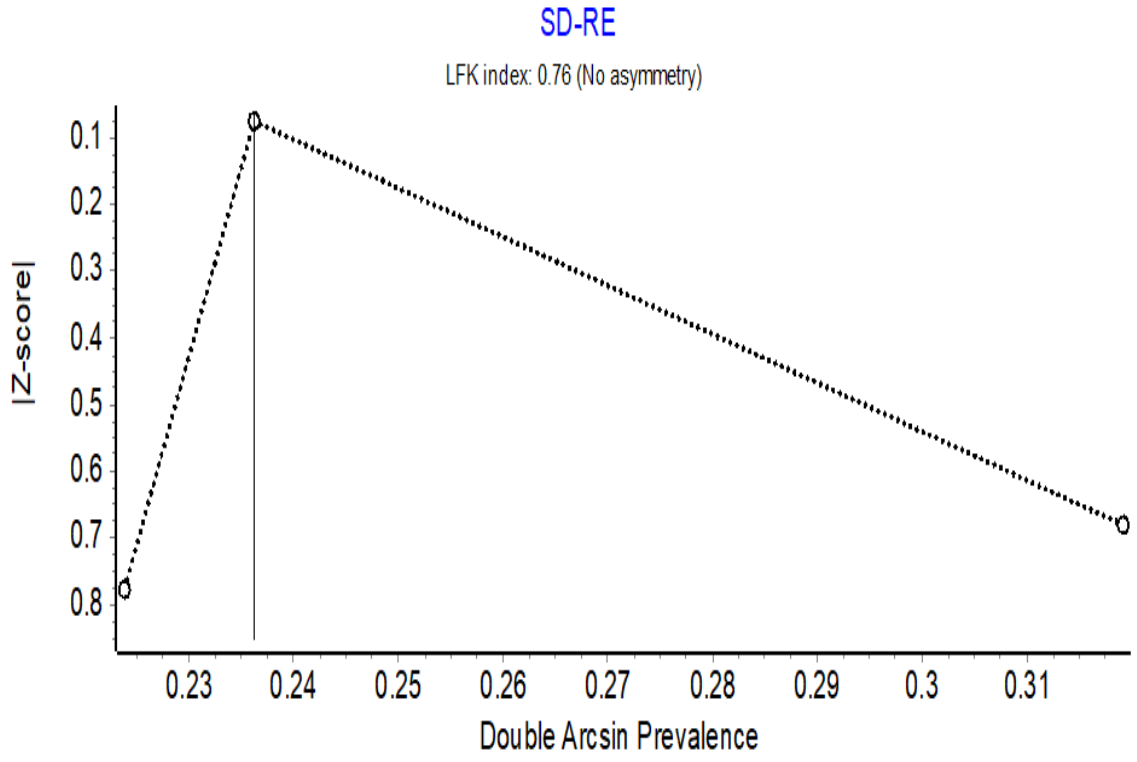

Figure 4. 11 Doi plot and LFK index of publication bias for shoulder dystocia.

4.4.4 Perinatal mortality

Five studies reported on the prevalence of perinatal mortality. Two of the studies conducted in India and Taiwan reported a 0% prevalence (Uma *et al.*, 2017; Wu *et al.*, 2016). A study conducted in Viet Nam reported a low prevalence of 1% (95%CI: 0 to 1) (Hirst *et al*., 2012) and the highest reported prevalence of 4% (95%CI: 3 to 6) was recorded in Belgium (Oriot *et al.*, 2018). A random-effects meta-analysis yielded an overall prevalence of 1% (95%CI: 0 to 3) with a significant heterogeneity observed (I^2 = 92%) (Figure 4.12). A funnel plot including all studies on perinatal mortality was generated (Figure 4.13) and the Doi plot for publication bias showed minor asymmetry (LFK index = 1.70) (figure 4.14) which could be an indication of possible publication bias.

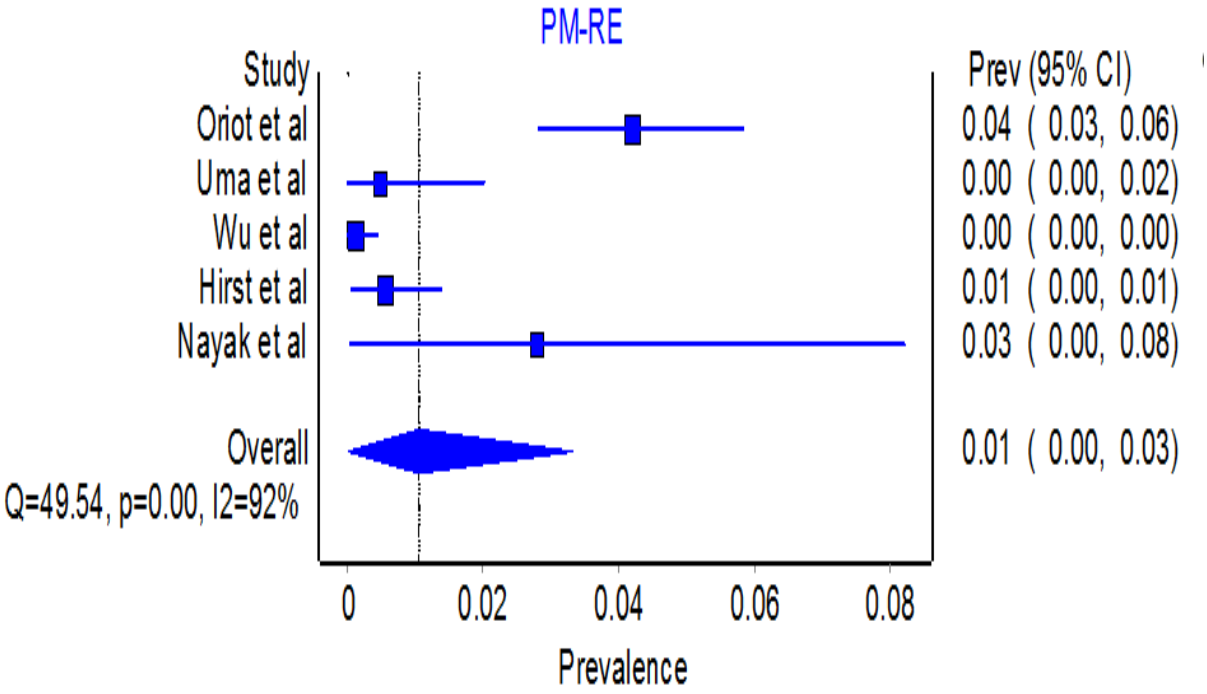

Figure 4. 12 Forest plot showing the meta-analysis for the prevalence of perinatal mortality.

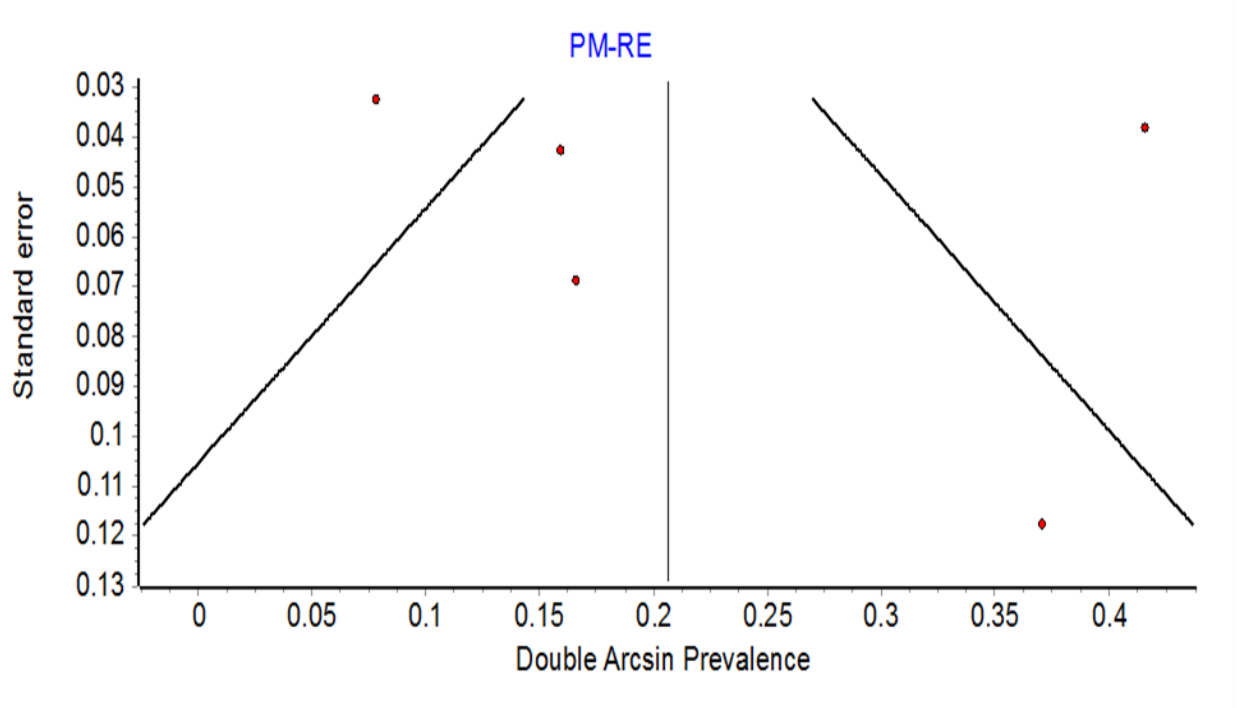

Figure 4. 13 Funnel plot for perinatal mortality.

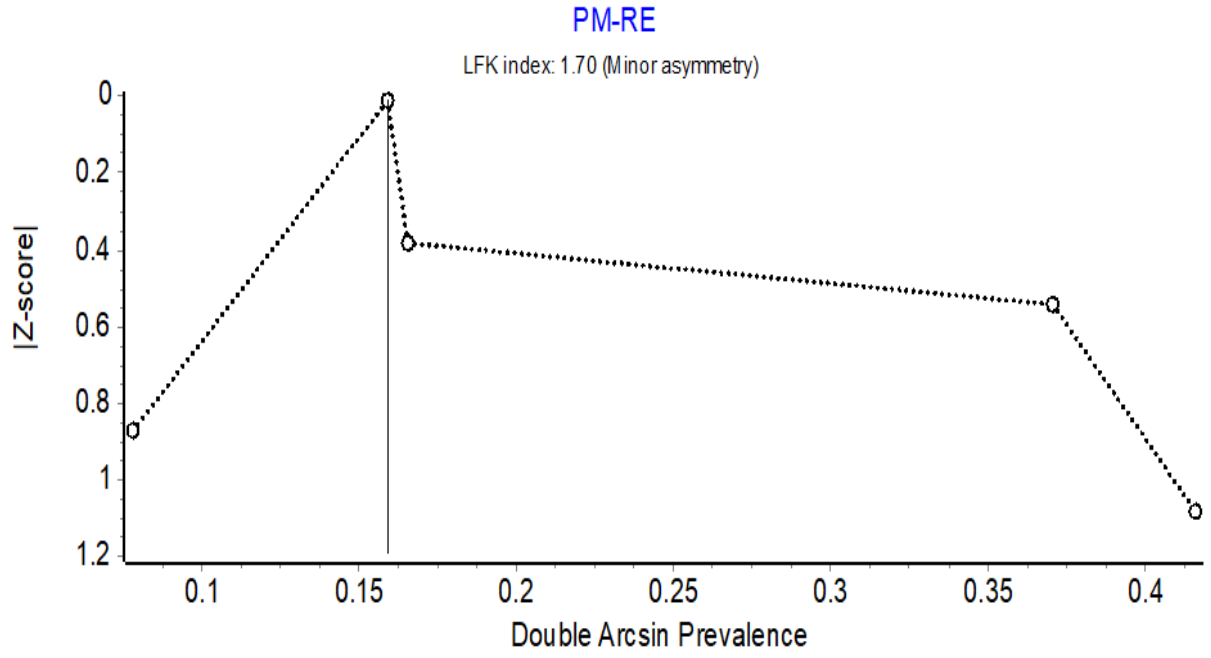

Figure 4. 14 Doi plot and LFK index of publication bias for perinatal mortality.

4.4.5 Neonatal hypoglycaemia

Ten studies reported on the prevalence of neonatal hypoglycaemia with the lowest prevalence of 1% (95%CI: 0 to 1) seen with the studies conducted in the United States and Taiwan (Wu *et al*., 2016; Sacks *et al*., 2015) and 1% (95%CI: 0 to 2) in China (Liao *et al*., 2014). Two studies showed similar results with the highest prevalence of 3% (95%CI: 1 to 6) in India (Uma *et al*., 2017) and 3% (95%CI: 0 to 7) in the United States of America (March *et al*., 2016). Random-effects analysis indicated an overall prevalence of 2% (95%CI: 1 to 2) with little heterogeneity between the studies (I^2 = 62%) (Figure 4.15). A funnel plot including all studies on neonatal hypoglycaemia was generated (Figure 4.16) and the Doi plot for publication bias showed major asymmetry (LFK index = 2.17) (Figure 4.17) which could indicate possible publication bias.

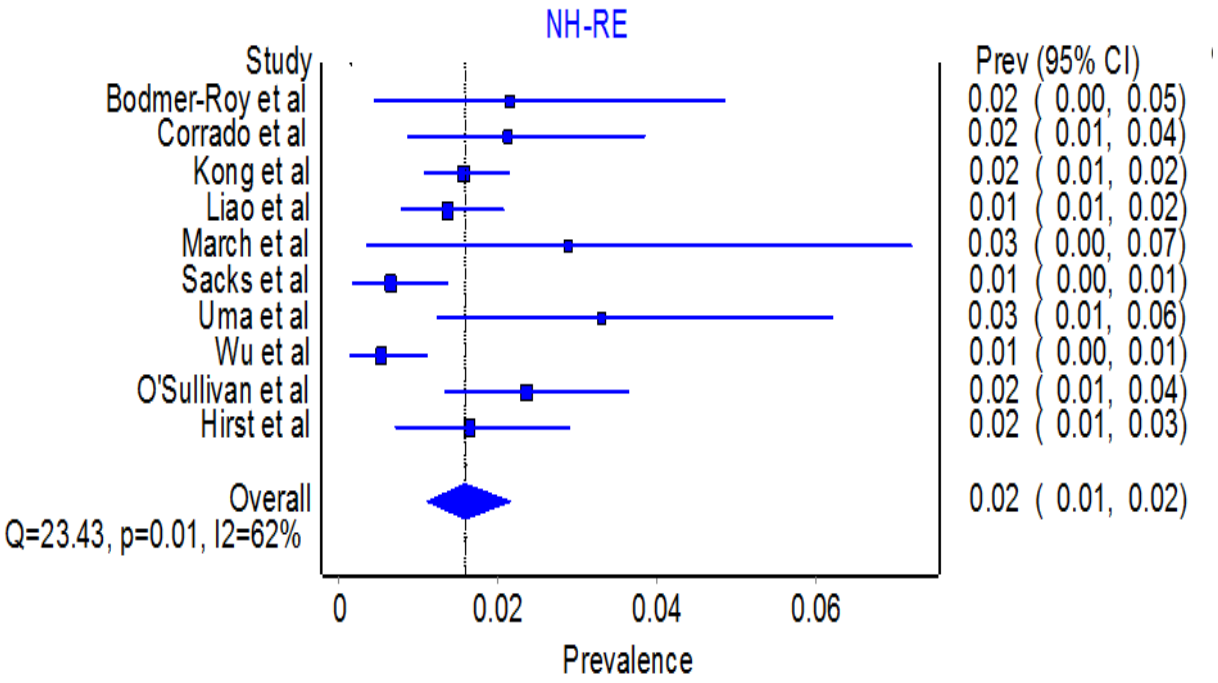

Figure 4. 15 Forest plot showing the meta-analysis for the prevalence of neonatal hypoglycaemia.

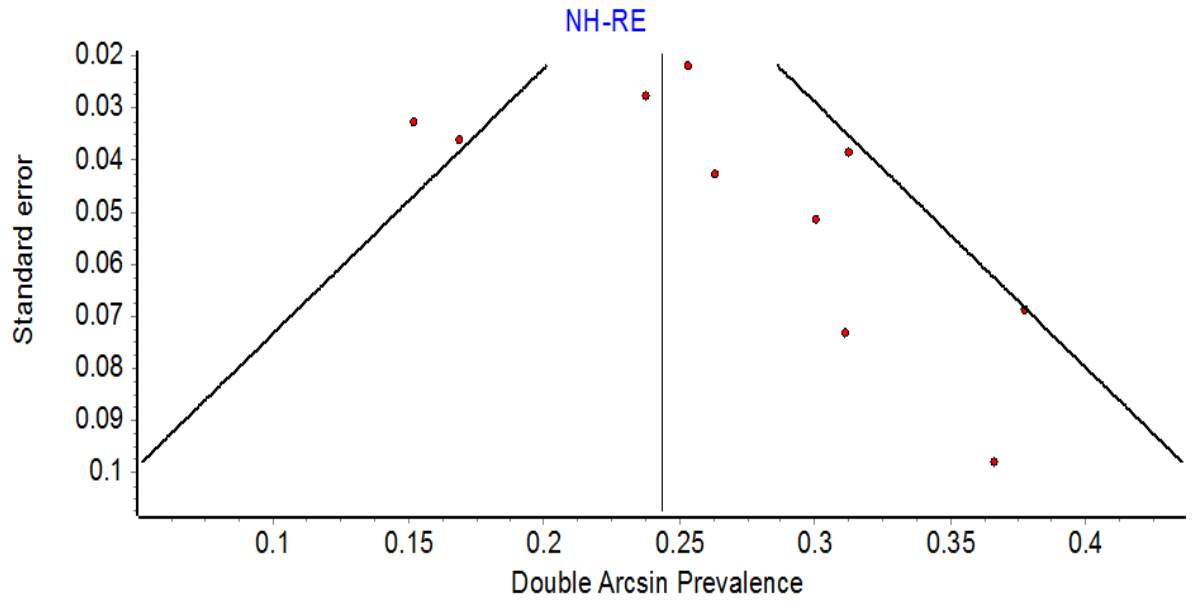

Figure 4. 16 Funnel plot for neonatal hypoglycaemia.

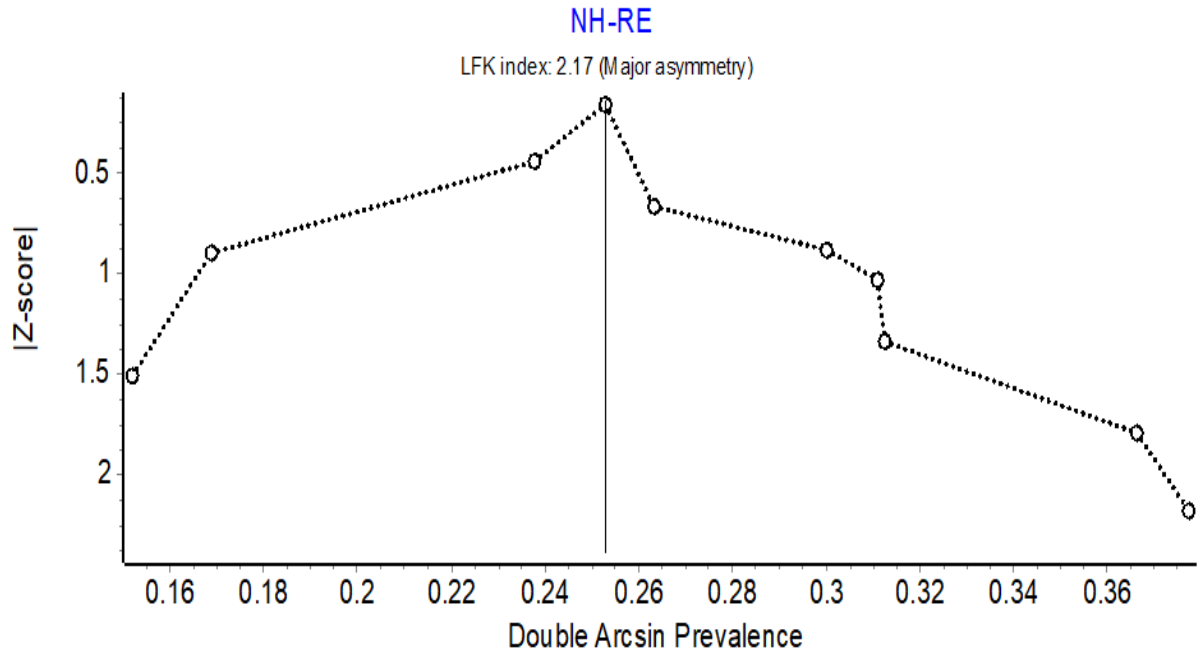

Figure 4. 17 Doi plot and LFK index of publication bias for neonatal hypoglycaemia.

4.4.6 Respiratory distress syndrome (RDS)

Three studies reported the prevalence of RDS which ranged from a minimum of 2% (95%CI: 1 to 3) in the United States of America (Sacks *et al*., 2015) to a maximum of 4% (95%CI: 2 to 5) in Ireland (O'Sullivan *et al.*, 2011) and 4% (95%CI: 1 to 10) in India (Nayak *et al.*, 2013). A random-effects meta-analysis yielded an overall prevalence of 3% (95%CI: 1 to 5) with little heterogeneity between the studies (I^2 = 60%) (Figure 4.18). A funnel plot including all studies on RDS was generated (Figure 4.19) and the Doi plot for publication bias showed no asymmetry (LFK index = 0.96) (Figure 4.20). Therefore, publication bias is unlikely.

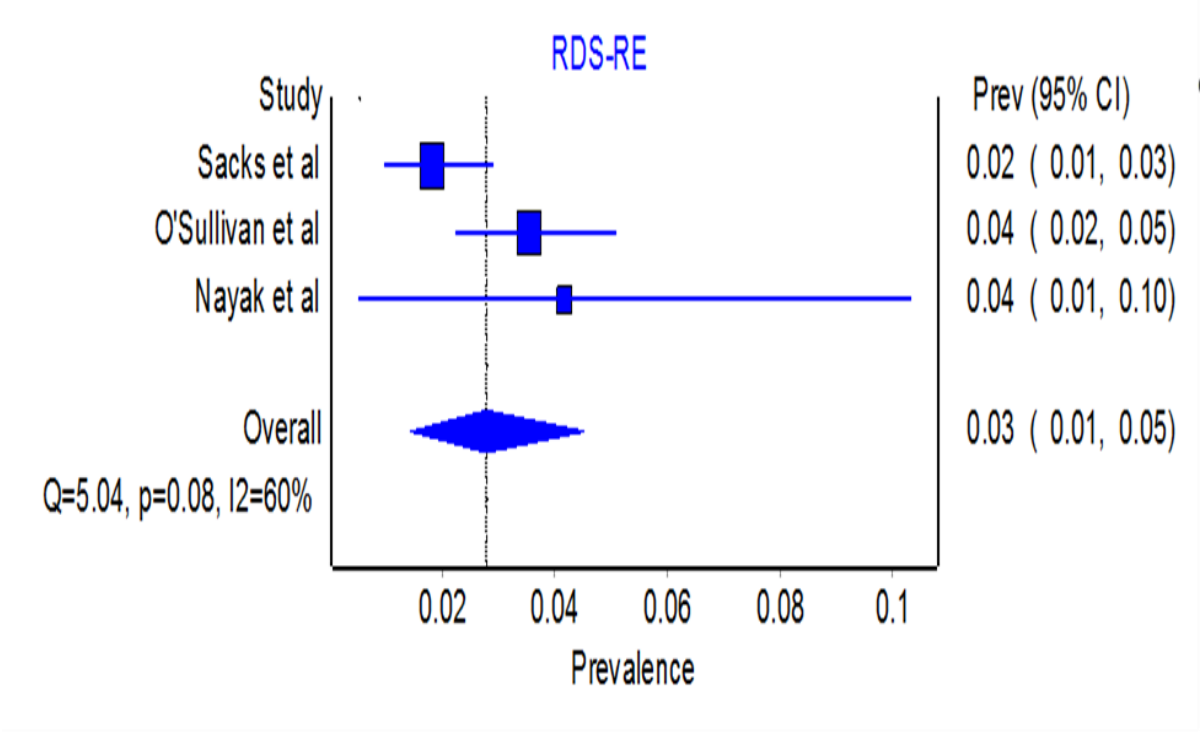

Figure 4. 18 Forest plot showing the meta-analysis for the prevalence of RDS.

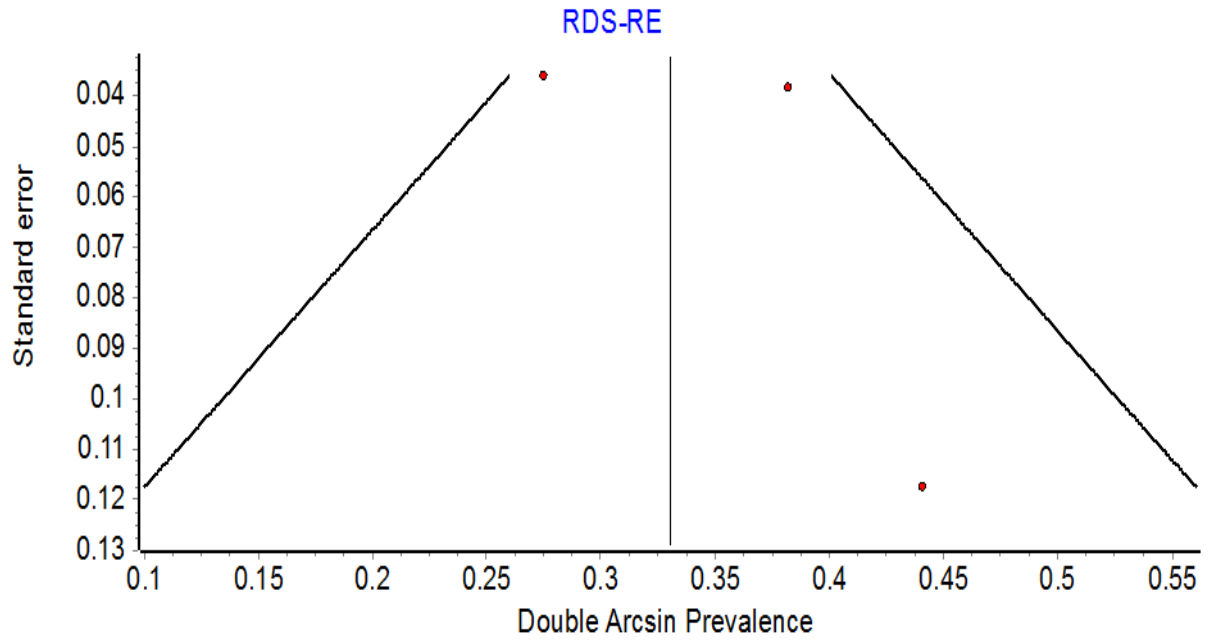

Figure 4. 19 Funnel plot for RDS.

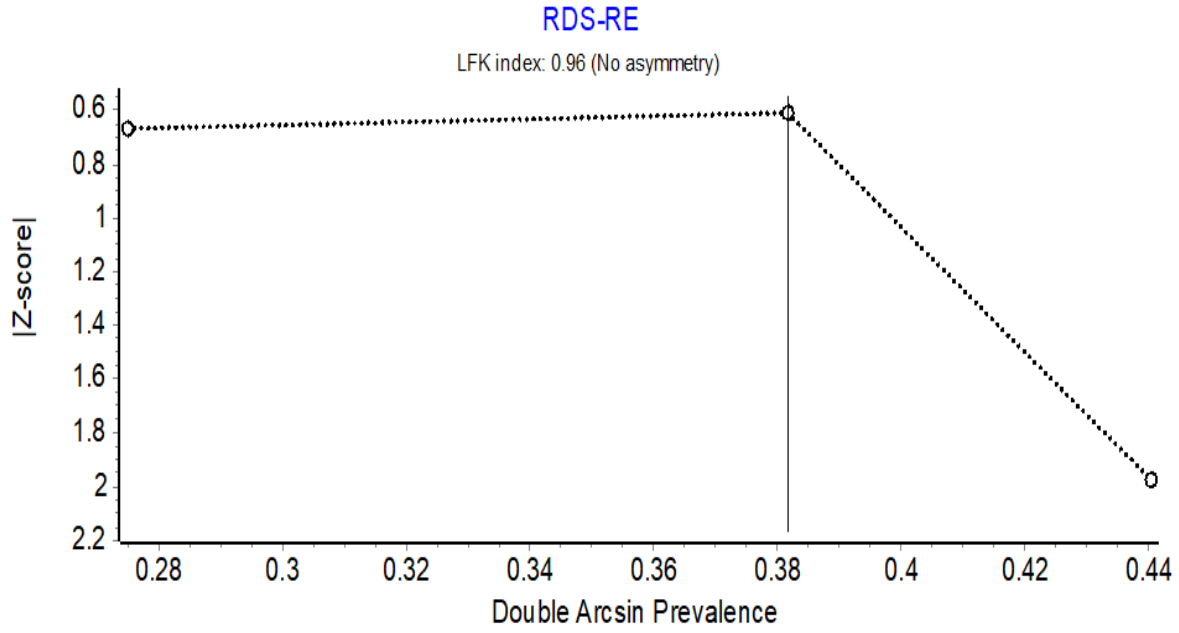

Figure 4. 20 Doi plot and LFK index of publication bias for RDS.

4.5 Chapter summary

All the publications included in this systematic review were observational studies, and only 15 publications from the search were used. The lowest number of participants from the included publications was 83, whereas the largest group size was 25,543 participants. Only the prevalence of foetal outcomes from mothers diagnosed with either WHO 2013 criteria or the IADPSG 2010 guideline was evaluated and the review found that the pooled prevalence of the foetal outcomes ranged from 1% to 11%. The subsequent chapter contains a detailed discussion of the findings in the current chapter.

Table 4.3: Summary of results

Relevant parameters	Primary outcome			Secondary outcome		
	Macrosomia	LGA	Perinatal mortality	Shoulder dystocia	Neonatal hypoglycaemia	RDS
I^2	98%	98%	92%	42%	62%	60%
Overall prevalence	7%	11%	1%	2%	2%	3%
LFK index	-0.51	-1.56	1.70	0.76	2.17	0.96
Overall 95% CI	2 to 13	6 to 16	0 to 3	1 to 3	1 to 2	1 to 5

CHAPTER 5

DISCUSSION

5.1 Introduction

This systematic review was carried out to evaluate the prevalence of adverse foetal outcomes in GDM using the WHO 2013 and/or IADPSG 2010 diagnostic criteria. Fifteen studies with 88,831 pregnant women (range: 83–25,543) from 12 countries around the world were included in this review and they showed a wide variation in the prevalence of foetal outcomes in GDM using the stipulated criteria. Studies were unevenly distributed geographically with six of them conducted in Asia, four in Europe, four in North America, one in Australia and non from Africa, Antarctica or South America. This is the final chapter of this systematic review and it presents a discussion of the findings along with the limitations of the study and recommendations thereof.

5.2 Prevalence of foetal outcomes in GDM

This study found strong evidence of heterogeneity, with high and significant I^2 results for all outcomes except for shoulder dystocia. Differences in ethnicity, maternal age and BMI disparities amongst the studies might have largely contributed to the heterogeneity of this prevalence and even though random-effect models were used in this meta-analysis, it is still hard to explain these differences. Subgroup analysis was not done due to the paucity in data availability.

For this study, only the risk of bias assessment was used in assessing the quality of the included studies. Each of the ten parameters in the risk of bias tool was allocated an equal weight and all the included studies in the final review were of either moderate or high risk of bias. The overall assessment of bias was dependent on the number of high-risk parameters out of the ten parameters. The results from the risk of bias assessment showed that most of the included

studies were not a complete representation of the national population, therefore, this limits the generalizability of the prevalence estimates obtained from this systematic review. Selection bias cannot be excluded; however, the small number of studies included is likely due to the strict inclusion criteria for the study, as well as the fact that very few studies applied the WHO 2013 and/or the IADPSG 2010 criteria for the definition of GDM-related foetal outcomes.

To our knowledge, this is the first meta-analysis evaluating the prevalence of adverse foetal outcomes of GDM using the WHO 2013 and/or IADPSG 2010 diagnostic criteria specifically for the following outcomes; macrosomia, LGA, shoulder dystocia, perinatal mortality, neonatal hypoglycaemia and RDS. This meta-analysis determined a pooled prevalence of 7% for macrosomia which was higher than the 6.5% reported by Bedu-Addo et al., (2020) from a hospital-based cross-sectional study of 200 women with singleton pregnancies in the Eikwe region of Ghana. The study by Bedu-Addo *et al* however did not specify if GDM mothers were included or excluded in the study population. A systematic review and meta-analysis including 40 studies published between 1999 and 2016 with a total of 106, 665 births using the random effect model reported an overall prevalence of 5.2% for macrosomia (Maroufizadeh *et al*., 2017). However, this study included heterogeneous studies of pregnant women with other risk factors such as obesity and maternal haemoglobin concentration which could have skewed the results. Another ecological study carried out in Brazil including all live new-borns from singleton pregnancies from 22 gestational weeks showed a 5.3% prevalence in 1,606,330 births and 5.1% prevalence in 422,069 births during the periods of 2001–2010 and 2012–2014 respectively (Nascimento *et al*., 2017). The differences in prevalence reported in this meta-analysis and that of the other studies could be due to the ethnic and geographic diversity in our study. It could also be as a result of the inclusion of mothers with other risk factors found in these other studies. The impact of these factors is supported by a report by Nizard and Ville (2009) that macrosomia frequency differs significantly by country and the type of diabetes mellitus. However, it is important to note that none of the three studies mentioned above indicated the diagnostic criteria used in their diagnosis of GDM, although, the threshold for macrosomia diagnosis (BW ≥4000g) used in these studies were the same as those used in our analysis. The variation in the prevalence may also be due to the difference in the sample size of the studies and our study.

For LGA, this systematic review showed an overall prevalence of 11%. Of all the outcomes evaluated in this review, the LGA was the outcome with the highest prevalence. A retrospective analysis of 6727 pregnancies by Benhalima *et al*. (2013) evaluated women previously classified

as normal by Carpenter Coustan (CC) criteria but later diagnosed as gestationally diabetic using IADPSG. They compared the result from the IADPSG group with the CC GDM group and women with normal glucose tolerance (NGT). From their analysis, it was found that LGA occurred in 10.8% of the IADPSG group, 13.8% of the CC group and 9.0% of the NGT group. The reason for the lower rate of LGA in the IADPSG group compared to the CC group could be from the use of the IADPSG criteria (Benhalima *et al*., 2013). Their study showed that IADPSG detects milder GDM and therefore, is expected to present lower rates in the occurrence of LGA than the CC group. The similarity in the result from the IADPSG group and our findings can be correlated based on the diagnostic criteria used. Another large population-based cohort study conducted in China among 16896 non-GDM pregnant women aged 18-45 years estimating the prevalence of LGA found an incidence of 15.9% (Hua et al, 2020). This result is higher than ours, however, the observed difference in prevalence may be related to weight gain in GDM mothers which is a contributory factor to LGA (Weschenfelder *et al*. 2019). An analysis by HAPO study suggested that birth weight is more strongly associated with maternal body mass index (BMI) (Metzger *et al*., 2008) and this correlation would explain the high LGA prevalence reported in our review and the study by Hua *et al*.

We found an overall prevalence of 2%of shoulder dystocia, an outcome that is one of the main perinatal difficulties associated with the delivery of macrosomic babies. Even though there is no available literature on systematic reviews reporting on the prevalence of this outcome concerning the WHO 2013/IADPSG guidelines, a hospital-based study found a 1% prevalence from 19,878 pregnancies in Omani women (Al-Khaduri *et al*., 2014). This prevalence is similar to that reported in this meta-analysis, although, our study included a more diverse population than the study from Oman. Another study by Wahi *et al* (2011) evaluated the prevalence and outcomes of GDM from Jammu region, India in 2025 women at 24th to 28th week of gestation for a period of 1-year (December 2007 to November 2008). They diagnosed GDM using the Diabetes In Pregnancy Study Group India (DIPSI) guidelines and compared the foetal outcomes with the result from the non-diabetic control group and non-interventional untreated GDM group. Shoulder dystocia prevalence in their untreated group was found to be 6.45% and this was significantly higher than the result obtained from their treated GDM group, 1.2%. The difference in the result of Wahi *et al* untreated group and our findings may be correlated to the findings from a systematic review and meta-analysis by Horvath et al. (2010) which showed that women who received treatment for GDM have significantly less incidence of shoulder dystocia. Another reason for the difference may be due to the different criteria used in their study and ours for GDM diagnosis. Wahi *et al.* used the DIPSI guideline while our study used

the WHO 2013 and/or IADPSG 2010 guidelines. This consequently impacts the prevalence of shoulder dystocia.

An overall prevalence of 1% (95%CI: 0 to 3) for perinatal mortality was found in this meta-analysis. In the large cohort study (HAPO), only 130 (0.56%) of the 23,316 deliveries experienced a perinatal death (HAPO 2008). Their result is comparably lower than ours but shows that the IADPSG criteria cut-off values may significantly increase the detection of GDM (Oriot *et al*., 2018), but not the prevalence of perinatal death. Another study from September 2012 to October 2014 involving 24,656 pregnancies across 198 facilities in India found the prevalence of Perinatal mortality to be 3.3 times higher than the prevalence of GDM (14.42%) found in their study using DIPSI and FOGSI guidelines (Jain, Pathak and Kotecha, 2014). Intuitively, the variation in the prevalence reported in our meta-analysis and the study by Jain *et al* could be vested in the criteria used to diagnose GDM. Jain *et al* used a single abnormal value approach while our meta-analysis used the 3-values OGTT approach.

The pooled prevalence of neonatal hypoglycaemia was 2% (95%CI: 1 to 2) in this meta-analysis. According to Johnson (2003), neonatal hypoglycaemia is a common problem affecting 3 to 29% of all pregnancies in different settings. As seen, the pooled prevalence of this study was out of this range. Najati and Saboktakin (2010) in a prospective study involving 14,168 deliveries at Tabriz Alzahra Teaching Hospital Iran, evaluated the new-borns during their first 24-hours of life and found a prevalence of 0.4% hypoglycaemic neonates. This was less than the 2.4% prevalence reported by Depuy *et al*. (2009) in a matched case-control study of 6416 terms, singleton infants and nondiabetic pregnancies. On the contrary, a cross-sectional study that was conducted among 196 neonates in Ethiopia from June 17 to August 3, 2018, found a prevalence of 25% which is much higher than the prevalence from our analysis (Fantahun and Nurussen, 2020). The results from these studies are closer to the finding of this meta-analysis except for the latter, however, the difference in the prevalence of neonatal hypoglycaemia could be due to the change in glucose cut-off values used in defining hypoglycaemia. Our study was not specific on the time frame and cut-off value for diagnosing neonatal hypoglycaemia, however, Depuy *et al, as well as Najati and Saboktakin,* defined neonatal hypoglycemia as blood glucose level <50mg/dL (2.8mmol/L) and evaluated the new-borns for neonatal hypoglycaemia during their first 24-hours of life. On the other hand, Fantahun and Nurussen defined neonatal hypoglycaemia as blood glucose level <47mg/dL or (<2.6 mmol/L) in the first 48 hours of life. Swinnen *et al.* (2009) suggested that the cut-off

values have a major effect on the prevalence of hypoglycaemia, and this may have consequently affected the prevalence in our study and the other studies.

This meta-analysis determined a pooled prevalence of 3% (95%CI: 1 to 5) for RDS. This outcome is a dominant clinical problem faced by preterm infants and is more frequent in male infants and infants of diabetic mothers (Pickerd and Kotecha, 2009). Nili and Mahdaviani (2004) found a prevalence of 8.2% for RDS among 4472 deliveries of which 107 (2.39%) infants were infants of diabetic mothers between January 2000 to January 2002 in Tehran, Iran. The prevalence from the infants of diabetic mothers is similar to our finding irrespective of the fact that congenital malformations were common in their group. Qaril *et al*., (2018) in a cross-sectional study involving 503 new-borns in 6 months (January to June 2016) in Saudi Arabia found a prevalence of 54.7%. Their study was not specific to babies of diabetic mothers but rather all neonates with respiratory distress were included in the study. The prevalence from the Qaril *et al* study was higher than the prevalence from this meta-analysis and the Nili and Mahdaviani study. The reason for such huge difference in prevalence could be due to a difference in parameters such as a history of hypertension, history of abruption placenta, and history of consanguinity that were identified in the mother and birth history of the study by Qaril *et al.* that were not in this metanalysis and that of Nili and Mahdavani.

5.3 The implication for clinical practice

The impact of the diagnostic criteria on the prevalence of GDM and the foetal outcomes cannot be over-emphasized, and the relationship between adverse foetal outcomes and GDM is, undoubtedly, complex regardless of the diagnostic criteria used in detecting the GDM. This study has demonstrated that the prevalence of adverse foetal outcomes of GDM according to the WHO 2013 and/or IADPSG 2010 diagnostic criteria are comparably low. These findings can be employed by health care practitioners to identify women with GDM as early as possible to target and support earlier interventions for the safe delivery and observation of babies delivered from these mothers. For example, induction of labour in women with suspected LGA or macrosomia, caesarean section for women with suspected LGA, macrosomia and shoulder dystocia.

5.4 The implication for public health practice

Knowledge about the prevalence of adverse foetal outcomes of GDM may be of substantial public health relevance. This systematic review has shown a comparably lower prevalence of adverse foetal outcomes of GDM. Therefore, the impact of GDM and its adverse outcomes on both mothers and their off-springs highlight the need and opportunity for health planners to develop integrated responses that could be used to inform the communities of the health implications of early diagnosis and expectancy from GDM. Education to the public on the impact of GDM and its adverse outcomes as well as regular testing is important to regulate the frequency of these outcomes. Also, monitoring the prevalence of foetal outcomes of GDM is essential to plan and organize health and social services and to assess the impact of potential preventive strategies.

5.5 Implication for research

This review fills an important gap in the literature and highlights that there is a comparably lower prevalence of adverse foetal outcomes associated with the diagnosis of GDM using the current WHO 2013 and/or IADPSG 2010 diagnostic criteria. The geographic distribution of the studies implies a dearth of research to inform context-specific findings in many low- and middle-income country (LMIC) settings where the burden of diabetes is high due to collision of epidemiological and demographic transitions, and where resources for GDM control are very scarce. This calls for more studies using these criteria in LMICs, by health care providers, to inform practice and resource allocation for control of GDM, especially in the African continent.

5.6 Limitations

The main limitation of this study is the paucity of published studies on the prevalence of foetal outcomes of GDM. Relevant publications were obtained using a search strategy that was based on the combination of various search terms adapted for each database. However, there may be a possibility of omitting certain publications that were not indexed properly under these terms as well as some unpublished data resulting in the identification of fewer studies. Another limitation

may be attributed to the searching of relevant publications by one author. This may have introduced selection bias. Also, the WHO 2013 and IADPSG 2010 would have resulted in expectedly fewer studies giving that these criteria were only recently established (less than 10-years old).

5.7 Conclusion

This systematic review has demonstrated that the prevalence of adverse foetal outcomes of GDM according to the WHO 2013 and/or IADPSG 2010 diagnostic criteria are comparably low. Due to the complications and risks of GDM to both expectant mothers and their babies, there is an urgent need for universal strategies for screening and diagnosing GDM. The use of a more uniform methodology should permit a more accurate estimation of the prevalence of foetal outcomes and facilitate comparisons across settings and populations. This will also help to address the true burden of adverse foetal outcomes from GDM. Further studies such as specifically designed prospective studies are therefore needed to evaluate these new diagnostic criteria and their association to GDM-related foetal outcomes in diverse settings and ethnic groups, particularly in low- and middle-income countries.

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APPENDIX I

Full-text articles excluded, with reasons.

Study	Reasons for exclusion
1. Mahanta *et al*., 2014	Did not use either WHO 2013 or IADPSG 2010.
2. Sreelakshmi *et al*., 2015	Did not use either WHO 2013 or IADPSG 2010.
3. Eren *et al*., 2015	Did not give information on outcomes of interest.
4. Falavigna *et al*., 2013	Did not use either WHO 2013 or IADPSG 2010. Used WHO 1999 for GDM diagnosis.
5. Feghali *et al*., 2018	Did not use either WHO 2013 or IADPSG 2010.
6. Hosseini *et al*., 2018	Used IADPSG for GDM diagnosis but did not give a clear indication of how many women had any of the outcomes of interest (exact cases were unknown).
7. Nakabuye *et al*., 2017	Used WHO 2013 diagnostic criteria but did not give relevant information on outcomes of interest.
8. Yu *et al*., 2019	Did not use either WHO 2013 or IADPSG 2010.
9. Lamminpää *et al*., 2016	Did not use either WHO 2013 or IADPSG 2010.
10. Sultana *et al*., 2010	Did not use either WHO 2013 or IADPSG 2010.